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5 ENDOCRINOLOGIC AND METABOLIC DRUGS

6 ADVISORY COMMITTEE (EMDAC)

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11 Wednesday, June 10, 2015

12 7:59 a.m. to 4:40 p.m.

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16 Hilton Washington DC North/Gaithersburg

17 620 Perry Parkway

18 Gaithersburg, Maryland

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1 C O N T E N T S

2 AGENDA ITEM PAGE

3 Call to Order and Introduction of Committee

4 Robert Smith, MD 12

5 Conflict of Interest Statement

6 Philip Bautista, PharmD 17

7 FDA Introductory Remarks

8 James Smith, MD, MS 22

9 **Applicant Presentations - Amgen, Inc.**

10 Introduction - Mechanism of Action

11 Rob Scott, MD 42

12 Unmet Need

13 Marc Sabatine, MD, MPH 51

14 Program Overview - Efficacy and Safety

15 Scott Wasserman, MD 66

16 Benefit-Risk

17 Rob Scott, MD 101

18 Clarifying Questions 113

19 **FDA Presentation**

20 Clinical Review of Efficacy and Safety

21 Eileen Craig, MD 133

22 Clarifying Questions 188

1 C O N T E N T S (continued)

2 AGENDA ITEM PAGE

3 Open Public Hearing 220

4 Clarifying Questions (continued) 257

5 Questions to the Committee and Discussion 294

6 Adjournment 396

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1 P R O C E E D I N G S

2 (7:59 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. SMITH: Good morning. Before we start,
6 I'd like to remind everyone to please silence your
7 cell phones or your smartphones, or any other
8 devices that may make signal noises, if you've not
9 already done that.
10 Also, I'd like to identify the FDA press
11 contact, Eric Pahon. If you're Eric -- there he
12 is, right in front.
13 My name is Robert Smith. I'm the
14 chairperson of the Endocrinologic and Metabolic
15 Drugs Advisory Committee, and I'll now call this
16 meeting of the committee to order.
17 We'll start by going around the table and
18 introducing ourselves, and let's start down here on
19 the right.
20 DR. ALBRECHT: I'm Helmut Albrecht, the
21 industry representative on the panel. I work for
22 H2A Associates, LLC, which is a pharmaceutical

1 consulting firm.

2 DR. COOKE: I'm David Cooke, an associate

3 professor of pediatrics at Johns Hopkins, and I'm

4 in the division of pediatric endocrinology there.

5 DR. STANLEY: I'm Charles Stanley. I'm a

6 pediatric endocrinologist at Children's Hospital

7 Philadelphia.

8 CAPT BUDNITZ: Dan Budnitz, director of

9 medication safety program at the Centers for

10 Disease Control and Prevention.

11 DR. ORZA: Michele Orza, I'm with the

12 Patient-Centered Outcomes Research Institute in

13 Washington, D.C., and I'm the acting consumer

14 representative.

15 MS. MCCALL: Debra McCall, and I'm the

16 patient representative.

17 DR. BURMAN: Ken Burman, chief of

18 endocrinology at MedStar Washington Hospital Center

19 and professor of medicine at Georgetown University.

20 DR. THOMAS: Abraham Thomas, senior vice

21 president and chairman of medicine at NYU Lutheran

22 in Brooklyn, New York.

1 DR. BLAHA: Morning. Mike Blaha. I'm the
2 director of clinical research for the Johns Hopkins
3 Ciccarone Center for the Prevention of Heart
4 Disease.
5 DR. BAUTISTA: Good morning. I'm Philip
6 Bautista. I'm the DFO for EMDAC.
7 DR. SMITH: And I'm Robert Smith. I'm a
8 professor of medicine and professor of public
9 health at Brown University. I'm an
10 endocrinologist, formerly was director of
11 endocrinology at the medical school at Brown. And
12 I'm chair of this committee.
13 DR. HIATT: William Hiatt. I'm a professor
14 of medicine at the University of Colorado School of
15 Medicine, division of cardiology with a specialty
16 in vascular medicine.
17 DR. WILSON: Peter Wilson, professor of
18 medicine and public health at Emory University,
19 endocrinology and preventive cardiology and
20 epidemiology.
21 DR. ROSENBERG: Good morning. I'm Yves
22 Rosenberg. I'm the chief of atherothrombosis and

1 coronary heart disease branch of the National
2 Heart, Lung and Blood Institute of the NIH in
3 Bethesda. I'm a preventive medicine physician and
4 clinical trialist.
5 DR. SHAMBUREK: I'm Bob Shamburek. I'm in
6 the lipoprotein metabolism section. I run the
7 lipid clinic in the intramural NHLBI at NIH.
8 DR. SAGER: Philip Sager. I'm consulting
9 professor of medicine in the department of
10 cardiology at Stanford University.
11 DR. NASON: Martha Nason. I'm a
12 biostatistician at the National Institute of
13 Allergy and Infectious Diseases.
14 DR. CRAIG: Eileen Craig, clinical reviewer,
15 Division of Metabolism and Endocrinology Products.
16 DR. J. SMITH: Jim Smith, deputy division
17 director, Division of Metabolism and Endocrinology
18 Products.
19 DR. GUETTIER: Jean-Marc Guettier, division
20 director, Division of Metabolism and Endocrinology
21 Products.
22 DR. ROSEBRAUGH: Curt Rosebraugh, director,

1 Office of Drug Evaluation II.

2 DR. SMITH: Thank you.

3 For topics such as those being discussed at

4 today's meeting, there are often a variety of

5 opinions, some of which are quite strongly held.

6 Our goal is that today's meeting will be a fair and

7 open forum for discussion of these issues and that

8 individuals can express their views without

9 interruption.

10 Thus, as a gentle reminder, individuals will

11 be allowed to speak into the record only if

12 recognized by the chairperson. We look forward to

13 a productive meeting.

14 In the spirit of the Federal Advisory

15 Committee Act and the Government in the Sunshine

16 Act, we ask that the advisory committee members

17 take care that their conversations about the topic

18 at hand take place in the open forum of the

19 meeting.

20 We are aware that members of the media are

21 anxious to speak with the FDA about these

22 proceedings. However, FDA will refrain from

1 discussing the details of this meeting with the
2 media until its conclusion Also, the committee is
3 reminded to please refrain from discussing the
4 meeting topic during breaks or lunch. Thank you.
5 Now, I'll pass the microphone to Phil
6 Bautista, who will read the Conflict of Interest
7 Statement.

8 **Conflict of Interest Statement**

9 DR. BAUTISTA: Thank you.
10 The FDA is convening today's meeting of the
11 Endocrinology and Metabolic Drugs Advisory
12 Committee under authority of FACA 1972. With the
13 exception of the industry representative, all
14 members and temporary voting members of the
15 committee are SGEs or regular federal employees
16 from other agencies and are subject to federal
17 conflict of interest laws and regulations.
18 The following information on the status of
19 this committee's compliance with federal ethics and
20 conflict of interest laws, covered by but not
21 limited to those found in 18 U.S.C. Section 208, is
22 being provided to participants in today's meeting

1 and to the public.

2 FDA has determined that members and

3 temporary voting members of this committee are in

4 compliance with federal ethics and conflict of

5 interest laws. Under Section 208, Congress has

6 authorized FDA to grant waivers to SGEs and regular

7 federal employees who have potential financial

8 conflicts when it's determined that the agency's

9 need for a particular individual's services

10 outweighs his or her potential financial conflict

11 of interest.

12 Related to the discussion of today's

13 meeting, members and temporary voting members of

14 this committee have been screened for potential

15 financial conflicts of interest of their own as

16 well as those imputed to them, including those of

17 their spouses or minor children and, for the

18 purposes of 18 U.S.C. Section 208, their employers.

19 These interests may include investments,

20 consulting, expert witness testimony, contracts,

21 grants, CRADAs, teaching, speaking, writing,

22 patents and royalties, and primary employment.

1 Today's agenda involves the discussion of
2 the safety and efficacy of BLA 125522, proposed
3 trade name Repatha, established name evolocumab,
4 for injection, submitted by Amgen, Incorporated, as
5 adjunct to diet to reduce LDL-C, total cholesterol,
6 ApoB, non-HDL-C, total cholesterol and HDL-C,
7 ApoB/ApoA1, VLDL-C, triglyceride, and
8 lipoprotein A; and to increase HDL-C and ApoA1 in
9 adults with hyperlipidemia or mixed dyslipidemia,
10 either in combination with a statin or statin with
11 other lipid-lowering therapies, including
12 ezetimibe, or alone, or in combination with other
13 lipid-lowering therapies in patients who are statin
14 intolerant, or alone or in combination with other
15 lipid-lowering therapies in patients for whom a
16 statin is not considered clinically appropriate.
17 In addition, the committee will discuss the
18 safety and efficacy of evolocumab to reduce LDL-C,
19 total cholesterol, ApoB, and non-HDL-C, in
20 combination with other lipid-lowering therapies,
21 for example, statins and LDL apheresis, in patients
22 at least 12 years of age with homozygous familial

1 hypercholesterolemia.
2 This is a particular matters meeting during
3 which specific matters related to Amgen's
4 evolocumab will be discussed. Based on the agenda
5 for today's meeting and all financial interests
6 reported by the committee members and temporary
7 voting members, no conflict of interest waivers
8 have been issued in connection with this meeting.
9 To ensure transparency, we encourage all
10 standing committee members and temporary voting
11 members to disclose any public statements that they
12 have made -- they might have made -- concerning the
13 product at issue.
14 With respect to FDA's invited industry
15 representative, we'd like to disclose that
16 Dr. Helmut Albrecht is participating in this
17 meeting as a non-voting industry representative
18 acting on behalf of regulated industry.
19 Dr. Albrecht's role in this meeting is to
20 represent industry in general and not any
21 particular company. Dr. Albrecht is employed by
22 H2A Associates and Alitair Pharmaceuticals.

1 We'd like to remind members and temporary
2 voting members that if the discussions involve any
3 other products or firms not already on the agenda
4 for which an FDA participant has a personal or an
5 imputed financial interest, the participants need
6 to exclude themselves from such involvement, and
7 their exclusion will be noted for the record.
8 FDA encourages all other participants to
9 advise committee of any other financial
10 relationships that they may have with the firm at
11 issue. Thank you.
12 DR. SMITH: Thank you. So we'll now proceed
13 with the FDA's introductory remarks from Dr. James
14 Smith.
15 DR. ORZA: While he's coming up, can I ask a
16 quick point of order?
17 DR. SMITH: Yes, Dr. Orza?
18 DR. ORZA: We all made statements yesterday
19 that could be seen to relate to this, the issues at
20 hand in this drug. Is it safe to assume that we
21 don't have to reiterate those because --
22 DR. SMITH: This is a totally separate

1 proceeding, on a totally separate drug, from a
2 totally separate sponsor, with a totally separate
3 submission. So I would say that we have perhaps
4 some things we learned yesterday in the field, but
5 that this is an independent proceeding that should
6 be, I would say, approached by that.
7 Any further comment from FDA on that?
8 DR. J. SMITH: I'll address that to some
9 extent in just a minute.
10 DR. SMITH: Thank you, Dr. Smith.
11 **FDA Introductory Remarks - James Smith**
12 DR. J. SMITH: Good morning. My name is Jim
13 Smith, and I'd like to thank many of you for being
14 with us again today. Because you've heard much of
15 what I'm going to say yesterday morning, I want to
16 emphasize that the repetition is necessary. And to
17 the point that was just being made, the discussion
18 of evolocumab today is its own meeting, and it
19 deserves just as much thought and discussion as you
20 all gave yesterday.
21 We may also have a different public audience
22 as well, so it's important for me and you to cover

1 similar materials since it applies to this
2 application as well. I will abbreviate my
3 introductory remarks to some extent, but I think
4 that I'm covering all of the same salient features.
5 So as you know, we entered the statin era in
6 1987 when a committee analogous to this one
7 recommended the approval of lovastatin or Mevacor.
8 And although there had been some discussion earlier
9 in that day regarding whether imaging-based
10 assessments of atherosclerosis should be required
11 prior to approval for lipid-modulating drugs.
12 Given the recognition the changes in
13 biomarkers such as LDL cholesterol may not always
14 translate into clinical benefit, the committee back
15 then ultimately recommended approval on the hope
16 that lovastatin would benefit patients; and they
17 certainly recognized that the drug had the
18 potential for use among millions of patients. And
19 they knew that off-target effects could offset the
20 expected clinical benefits from their experience
21 with Clofibrate in the then recently completed
22 World Health Organization Cooperative trial, or

1 even with estrogen and dextrothyroxine in the
2 coronary drug project as just a couple of examples.
3 Now, despite that uncertainty, lovastatin
4 was approved, and it was not until the 1994
5 publication of the 4S trial, however, that the
6 lowering of LDL cholesterol by a statin was shown
7 to reduce the risk of adverse cardiovascular
8 events. And as you know, this was the first of
9 multiple cardiovascular outcomes trials that have
10 robustly demonstrated that statins reduce
11 cardiovascular events in a variety of patient
12 populations.
13 Now, according to the CTT Collaboration's
14 meta-analysis of statin trials, each approximate
15 40- milligram per deciliter reduction in LDL
16 cholesterol reduces the risk for major
17 cardiovascular events by approximately 22 percent.
18 Now, once again LDL-C has been referred to
19 as a validated surrogate endpoint since
20 statin-reduced reductions in LDL cholesterol have
21 been shown in multiple clinical trials to be
22 associated with reduced cardiovascular risk.

1 FDA has defined a surrogate endpoint as a
2 marker such as a laboratory measurement or physical
3 sign that is used in therapeutic trials as a
4 substitute for a clinically meaningful endpoint
5 that is a direct measure of how a patient feels,
6 functions, or survives and is expected to predict
7 the effect of therapy.
8 Note that such an endpoint is considered a
9 valid surrogate only if the drug's effect on the
10 surrogate leads to a clinical benefit. Now, the
11 regulatory use of a surrogate depends on the
12 evidence that a drug's effect on the surrogate
13 predicts clinical benefit.
14 When a drug's effect on a surrogate marker
15 is known to predict clinical benefit, it can be
16 used for traditional or full approval. If the
17 drug's effect on the marker is only reasonably
18 likely to predict clinical benefit, accelerated
19 approval might be an option.
20 Once again, it is important to understand
21 that risk factor and surrogate are not synonymous.
22 As I mentioned yesterday, there are numerous

1 examples of drugs that have led to favorable
2 changes in a risk factor, but those changes have
3 not translated into the expected benefits with
4 regard to clinical outcomes.
5 Since many people have questions about
6 accelerated approval, I'm going to remind you again
7 what it is. This is a potential approval pathway
8 for drugs intended to treat a serious or
9 life-threatening disease or condition that is based
10 on substantial evidence of a drug's effect on a
11 surrogate endpoint that is at least reasonably
12 likely to predict clinical benefit.
13 For drugs granted accelerated approval,
14 postmarketing confirmatory trials have been
15 required to verify and describe the anticipated
16 effect on clinical outcomes. And as I explained
17 yesterday, FDA has never used this regulatory
18 pathway for the approval of lipid-modulating drugs.
19 The cardiovascular outcomes trials that have
20 been conducted to confirm the clinical benefits of
21 the statins were not regulatory requirements.
22 These trials could have failed to show evidence of

1 benefit on clinical outcomes, and it's entirely
2 plausible that the approvals and indications would
3 not have been withdrawn. Thankfully, we did not
4 have that scenario with the statins.
5 As you know, approval of drugs based on LDL
6 cholesterol without evidence for benefit on
7 clinical outcomes has not been without controversy.
8 The last first-in-class LDL-lowering drug for
9 widespread use was Zetia in October of 2002, and
10 the approvability of Zetia was not discussed with a
11 committee such as yourselves.
12 LDL cholesterol was considered a validated
13 surrogate, and the mechanism of action and safety
14 profile of Zetia did not raise concerns at the time
15 of approval that would have led the agency to
16 believe that the net clinical benefit could be
17 unfavorable.
18 As you know, the lack of cardiovascular
19 outcomes data became especially controversial after
20 the publication of the ENHANCE and SEAS trials in
21 2008, which raised concerns regarding both the
22 clinical benefits and risks of ezetimibe.

1 This emphasizes an important point.
2 Approval based on a surrogate endpoint always
3 leaves uncertainty regarding true clinical benefit,
4 which can create challenges when safety concerns
5 arise.
6 The long awaited IMPROVE-IT trial, which
7 studied the effect of adding ezetimibe to
8 simvastatin on cardiovascular outcomes among more
9 than 18,000 patients with acute coronary syndrome,
10 was published last week in the New England Journal
11 of Medicine. According to the investigators,
12 adding ezetimibe to simvastatin led to a
13 statistically significant reduction in the risk of
14 cardiovascular events of a magnitude that they
15 expected based on the degree of LDL lowering
16 achieved.
17 This trial has not been reviewed by FDA, and
18 we will need to make a regulatory decision
19 regarding the approval of evolocumab before we will
20 have had the opportunity to independently fully
21 review the results from IMPROVE-IT and their
22 potential implications.

1 Now, we note that there seems to be an
2 increasing emphasis on using therapies that have
3 proven clinical benefit, moving away from specific
4 biomarker targets. The recent cholesterol
5 guidelines from the ACC and AHA provide an example
6 of this paradigm shift, but we recognize that this
7 is controversial and that not all professional
8 societies have followed suit. And as I mentioned
9 yesterday, we are not here to debate the pros and
10 cons of various practice guidelines.
11 It does seem relevant, however, that we are
12 now evaluating the potential approval of a novel
13 LDL-lowering drug in the setting of widely
14 available drugs, the statins, that have proven
15 benefits on the very outcomes for which we're using
16 LDL cholesterol as a surrogate, as well as a very
17 well characterized safety profile for chronic use.
18 Now, in the excitement that surrounds the
19 potential availability of a new class of drugs, it
20 is incredibly important for us to remember that
21 relying on surrogates to establish clinical benefit
22 sometimes fails us. Off-target adverse effects

1 could led to net clinical harm even if we were
2 correct about the relationship between the
3 surrogate and the clinical benefit that it was
4 expected to predict.
5 Alternatively, sometimes we get the causal
6 relationship wrong. The example I cited yesterday,
7 although it's not the only one, was torcetrapib.
8 It's worth remembering that the magnitude of LDL
9 cholesterol reduction exhibited by torcetrapib
10 would have met the historical FDA benchmark for
11 approval based on LDL cholesterol alone.
12 Thankfully, we learned that torcetrapib
13 increased the risk of both cardiovascular events
14 and mortality in a pre-approval cardiovascular
15 outcomes trial. Although many believe that this
16 unfortunate outcome was the result of off-target
17 toxicity, this is a good example that it sometimes
18 takes an unexpected result to make us aware of
19 either the presence or the severity of such
20 off-target effects
21 One might ask then, like Dr. Hiatt did
22 yesterday, why aren't we asking you to consider

1 approval of the application being discussed today
2 under an accelerated approval paradigm where
3 confirmation of benefit on clinical outcomes would
4 be required in the postmarketing setting. And this
5 may seem especially attractive since the applicant
6 recently announced that they have fully enrolled a
7 27,500 patient cardiovascular outcomes trial, and
8 their briefing document states that the trial is
9 anticipated to conclude no later than 2017.
10 The answer in part is that we've never used
11 this regulatory pathway for a lipid-modulating drug
12 before, so there would be several regulatory
13 considerations that we would have to work through
14 to determine the feasibility of using this approval
15 pathway, and today is not the appropriate time for
16 those discussions.
17 Like yesterday, it would be most helpful for
18 you to focus your discussion on whether the LDL
19 cholesterol lowering induced by evolocumab is
20 sufficient to substitute for demonstrating its
21 effect on clinical outcomes in one or more
22 populations.

1 This is the question that we must answer
2 when considering whether to approve evolocumab
3 using the regulatory pathway that we have used for
4 LDL-lowering drugs in the past, and once again,
5 we'd like to hear your thoughts about it.
6 Now, I want to emphasize two important
7 points here. First, once again, by evolocumab, and
8 we're not asking you to discuss the benefits of
9 lowering LDL cholesterol by any drug that could
10 potentially be developed. Each drug may raise
11 different issues that may affect whether or not we
12 consider approval based on LDL cholesterol as a
13 surrogate endpoint.
14 Second, I'm once again stressing the words
15 "substitute for." We look forward to the results
16 of the applicant's cardiovascular outcomes trial,
17 but barring a safety concern, it is entirely
18 plausible that any approval based on LDL
19 cholesterol alone could remain regardless of
20 whether their outcomes trial establishes clinical
21 benefit or not.
22 As I stated yesterday, I'm sure the company

1 will do everything in their power to maintain trial
2 integrity. But if an approval and the availability
3 of the drug in the marketplace lead to patients
4 discontinuing from this placebo-controlled trial or
5 starting to take evolocumab outside of the trial's
6 protocol, we won't have control over that.
7 As I stated before, I cannot predict what
8 would happen to the approval or labeling if the
9 trial did not show the benefit of evolocumab on
10 cardiovascular events. After all, the trial is not
11 designed to test all of the populations for which
12 the applicant is seeking an indication such as
13 those with heterozygous or homozygous familial
14 hypercholesterolemia.
15 If the trial fails to meet its primary
16 objective, I'm fairly certain that the applicant
17 would argue that its results could not be
18 extrapolated to all clinical use scenarios.
19 A few years ago, we approved lomitapide and
20 mipomersen for homozygous familiar
21 hypercholesterolemia, or HoFH, based on the drugs'
22 effects on LDL cholesterol. Reductions in LDL

1 cholesterol were especially compelling as evidence
2 of benefit for this rare life-threatening disorder
3 in which the phenotype is the direct result of
4 abnormal LDL metabolism.
5 As you know, these patients have absent or
6 severely dysfunctional LDL receptors, leading to
7 extraordinarily high LDL cholesterol and premature,
8 aggressive cardiovascular disease that often
9 manifests in childhood.
10 When we discussed these applications with
11 our advisory committee, however, it was emphasized
12 that the position of LDL cholesterol as a surrogate
13 may be context dependent and that the committee's
14 discussion, revolving around the acceptance of LDL
15 cholesterol to establish benefit for those drugs,
16 should not be extrapolated to other clinical
17 scenarios.
18 So today, we are asking that you consider
19 the various potential uses for evolocumab
20 specifically and discuss for what patient
21 populations, if any, you are convinced that the
22 drug's effects on LDL cholesterol is sufficient by

1 itself to establish a clinical benefit. Of course,
2 as you know, HoFH is one of the populations in whom
3 evolocumab has been studied.
4 We discussed this yesterday, but I need to
5 repeat it again. Many are familiar with the
6 approval of drugs for diabetes or obesity for which
7 postmarketing cardiovascular outcomes trials have
8 been required. In those situations, the regulatory
9 requirement to conduct a cardiovascular outcomes
10 trial is to characterize safety, not to confirm
11 efficacy.
12 Since the passage of FDAAA, FDA can now
13 require postmarketing clinical trials to assess
14 serious risks or to identify unexpected serious
15 risks if specific statutory provisions are met. So
16 these trials that are being conducted under the
17 diabetes paradigm are intended to exclude a certain
18 degree of cardiovascular risk. They are not being
19 designed to confirm the clinical benefits expected
20 from drug-induced reductions in hemoglobin A1c, for
21 example.
22 I think it would make little sense to

1 require a safety trial to exclude increased
2 cardiovascular risk for a drug intended solely for
3 use to reduce cardiovascular risk. If we determine
4 that there are safety concerns with evolocumab that
5 warrant further study in a postmarketing trial,
6 then we might consider whether the applicant's
7 ongoing cardiovascular outcomes trial would provide
8 a platform to evaluate those concerns. But once
9 again, that's a different situation than requiring
10 an outcomes trial to confirm the benefit of a drug
11 on clinical outcomes after approval.
12 Now, I'll turn to the points that we're
13 going to ask you to discuss today so that you can
14 keep them in mind as you hear the presentation.
15 And once again, a few of these are going to sound
16 very familiar to those of you who were here
17 yesterday, but I need to ask you to try and erase
18 yesterday from your brain, to the extent you can.
19 Today's applicant deserves a robust
20 discussion of their product as well. So even if
21 you feel like you said what you had to say
22 yesterday, I'm going to ask you to participate

1 today again, so that we have your thoughts
2 documented as part of today's record for this
3 product as well, and if necessary, for the
4 applicant to respond to some of your concerns, to
5 state their opinion.
6 The first discussion point asks you to
7 discuss the safety of evolocumab as observed in the
8 clinical development program. Once again, we've
9 listed several of the topics that were investigated
10 as part of the safety review, but you should feel
11 free to raise any other concerns you may have as
12 well.
13 We're also asking you to discuss the
14 adequacy of the current clinical database to
15 characterize safety, and we'd like you to comment
16 on your level of concern regarding the safety of
17 achieving very low levels of LDL cholesterol
18 induced by evolocumab.
19 The second discussion point asks you to
20 discuss the applicant's two dosage regimens that
21 they selected to develop in phase 3. They
22 indicated to us that they wanted to appeal to

1 patient preference considerations, that is, some
2 patients may prefer to inject a larger volume,
3 which they're proposing to market as 3 injections
4 within a 30-minute period once monthly, versus a
5 smaller volume, that is, one injection every
6 2 weeks.
7 These two regimens, however, appear to
8 produce rather similar magnitudes of LDL
9 cholesterol reduction over the dosing interval. So
10 if a healthcare provider becomes uncomfortable with
11 the magnitude of LDL cholesterol reduction
12 achieved, they would either have to down-titrate
13 other lipid-modulating drugs such as a statin or
14 discontinue evolocumab. And we'd like you to
15 discuss whether you would have any concerns with
16 evolocumab not being labeled with dosage regimens
17 that provide varying degrees of LDL cholesterol
18 lowering if approved.
19 Third, evolocumab has been studied among
20 patients with HoFH. The applicant has proposed
21 that patients with HoFH ought to have an option to
22 increase the dosage to 420 milligrams every

1 2 weeks. Our reviewers are not convinced that
2 there is substantial evidence supporting the
3 incremental benefit of this higher dose, and the
4 safety database for this regimen is quite small, so
5 we'd like to hear what you think about it.
6 The fourth discussion point is central to
7 the discussion of benefit. The question is whether
8 LDL cholesterol is sufficient to substitute for
9 demonstrating the effect of evolocumab on clinical
10 outcomes in one or more populations.
11 As I told you yesterday, we don't want you
12 to feel restricted by precedent here or what the
13 applicant has proposed as an indication. We'd once
14 again like to hear a discussion regarding the
15 patient populations for whom you believe that
16 lowering LDL cholesterol with evolocumab would be
17 convincing enough evidence of a clinical benefit
18 that you wouldn't need to see data from a
19 cardiovascular outcomes trial to confirm that
20 benefit.
21 Last, we have two voting questions. First,
22 has the applicant sufficiently established that the

1 LDL cholesterol-lowering benefit of evolocumab
2 exceeds its risk to support approval in one or more
3 patient populations, excluding HoFH? And once
4 again, we're reminding you here that under the
5 current regulatory pathway, it would not be
6 required to successfully demonstrate an effect of
7 evolocumab on cardiovascular outcomes after such an
8 approval.
9 Similar to yesterday, we're not asking you
10 to vote on the exact indication that the applicant
11 has proposed, and that should not be taken as an
12 indication that we've rejected the applicant's
13 proposal.
14 We are confident that your discussions today
15 and your comments following the vote will provide
16 the advice we need as we move forward with this
17 application.
18 The second voting question is similar but
19 asks whether the applicant has established that the
20 LDL cholesterol-lowering benefit of evolocumab
21 exceeds its risk to support approval for HoFH.
22 So with that, I'd like to thank you-all once

1 again for your service today, and we look forward
2 to the discussion.
3 DR. SMITH: Thank you, Dr. Smith.
4 Both the Food and Drug Administration, the
5 FDA, and the public believe in a transparent
6 process for information-gathering and
7 decision-making. To ensure such transparency at
8 the advisory committee meeting, FDA believes that
9 it's important to understand the context of an
10 individual's presentation.
11 For this reason, FDA encourages all
12 participants, including the sponsor's non-employee
13 presenters, to advise the committee of any
14 financial relationships that they may have with the
15 firm at issue, such as consulting fees, travel
16 expenses, honoraria, and interests in the meeting.
17 Likewise, FDA encourages you at the beginning of
18 your presentation to advise the committee if you do
19 not have any such financial relationships.
20 If you choose not to address this issue of
21 financial relationships at the beginning of your
22 presentation, it will not preclude you from

1 speaking. And so, we will now proceed with the
2 presentations from Amgen.
3 **Applicant Presentation - Rob Scott**
4 DR. SCOTT: Thank you.
5 Good morning, everybody. My name is Rob
6 Scott. I'm the head of global cardiovascular,
7 metabolic and neuroscience development at Amgen.
8 I'd like to thank the FDA for the opportunity to
9 present the evolocumab program and welcome the
10 members of the committee and the public.
11 We are pleased to be able to present
12 evolocumab for the management of patients with
13 dyslipidemia. Following my brief introduction and
14 discussion of the mechanism of action of PCSK9
15 inhibition with a monoclonal antibody, Dr. Marc
16 Sabatine, a cardiologist from Brigham and Women's
17 Hospital and chairman of the TIMI study group, will
18 discuss the reason why an additional therapy for
19 lipid lowering is so crucial.
20 Dr. Scott Wasserman, the therapeutic area
21 head for cardiovascular and metabolic development
22 at Amgen, will present the data from our global

1 clinical program, and I will return to finish on
2 our assessment of the benefit/risk profile of
3 evolocumab.
4 Please note that this slide and the next
5 list the disclosures for external speakers.
6 During the question and answer session,
7 three additional experts will be available to
8 assist in answering the committee's questions.
9 Dr. Christie Ballantyne is an expert in the field
10 of familial hypercholesterolemia and the treatment
11 of hyperlipidemia. He is professor of medicine and
12 chief of the section of atherosclerosis and
13 vascular medicine at Baylor College of Medicine.
14 Dr. Evan Stein is an expert on familial
15 hypercholesterolemia with a special emphasis on
16 homozygous FH. Dr. Stein also has particular
17 expertise in lab methodology associated with the
18 measurement of lipids.
19 Dr. Janet Wittes is the president of
20 Statistics Collaborative and an expert on
21 statistical methodology in clinical trials.
22 As we will present this morning, evolocumab

1 is a fully human monoclonal antibody against PCSK9,
2 which blocks the interaction between this protein
3 and the LDL receptor. We are proposing that
4 evolocumab be indicated in two different patient
5 populations: firstly, in patients with familial or
6 non-familiar hyperlipidemia and mixed dyslipidemia,
7 and secondly, in patients with homozygous familial
8 hypercholesterolemia.
9 This is the indication we are proposing for
10 the first patient population. Evolocumab is
11 indicated in adults with primary heterozygous
12 familiar and non-familial hyperlipidemia or mixed
13 dyslipidemia as an adjunct to diet to reduce LDL
14 cholesterol in a variety of other atherogenic
15 lipoproteins in ratios, including lipoprotein(a).
16 Evolocumab is also indicated to raise HDL
17 cholesterol or ApoA1 in these subjects. This
18 indication is in combination with a statin or a
19 statin with other lipid-lowering therapies, or
20 alone or in combination in patients who are statin
21 intolerant or patients for whom a statin is not
22 considered clinically appropriate.

1 This is the indication we're proposing for
2 the second patient population. Evolocumab is also
3 indicated in adults or adolescents age 12 years or
4 more with homozygous familiar hypercholesterolemia
5 to reduce LDL cholesterol and other related
6 parameters in combination with other lipid-lowering
7 therapies such as statins or LDL apheresis.
8 The proposed dose and frequency varies with
9 these two populations. In primary hyperlipidemia
10 and mixed dyslipidemia, evolocumab can be dosed as
11 140 milligrams given every 2 weeks or
12 420 milligrams given once a month. Since these two
13 doses are clinically equivalent in terms of safety
14 and efficacy, the choice of dose is a matter of
15 patient preference and convenience.
16 In homozygous FH patients, evolocumab can be
17 dosed with 420 milligrams given every month. This
18 dose can be increased to 420 milligrams every
19 2 weeks based on response to therapy or to
20 synchronize therapy in those patients who are
21 undergoing apheresis twice monthly. Evolocumab is
22 administered by the patient at home using an auto

1 injector.

2 The story of PCSK9, proprotein convertase

3 subtilisin kexin type 9 -- and I promise not to say

4 that again in this meeting -- is a beautiful

5 scientific story rooted in genetics. In 2003,

6 Marianne Abifadel and colleagues identified a

7 family in France with high LDL and a pedigree of

8 early onset cardiovascular disease typical of

9 autosomal dominant hypercholesterolemia.

10 This family did not carry the expected

11 mutations in the LDL receptor or ApoB genes but had

12 a mutation that was later demonstrated to be a gain

13 of function mutation in PCSK9.

14 On the bottom of this slide, you can see

15 that there's a range of rare gain of function

16 mutations that can led to LDL levels of up to

17 350 milligrams per deciliter. On the lower

18 right-hand side are LDL levels as low as

19 53 milligrams per deciliter associated with the

20 more common loss of function mutations.

21 The R46L mutation is present in around

22 2 percent of the population and causes a modest

1 16 percent reduction of 17 milligrams per deciliter
2 of LDL on average.
3 The 16 percent reduction of LDL with a
4 common R46L mutation has been studied by several
5 different groups, and you can see that in five
6 different studies, there was a reduction in
7 myocardial infarction of 40 to 70 percent.
8 This larger than expected effect probably
9 represents the beneficial impact of lifelong lower
10 LDL levels. This kind of data is highly supportive
11 of trying to develop a PCSK9 inhibitor to reduce
12 cardiovascular risk.
13 PCSK9 is a protein expressed abundantly in
14 the liver, and it acts as a regulator of LDL
15 receptor expression. The following cartoons
16 illustrate the mode of action of PCSK9 inhibition
17 inside a liver cell. The orange area on the top
18 left represents the extra cellular space separated
19 from the intracellular space in pink by the cell
20 membrane in yellow.
21 When PCSK9 is absent, LDL receptors,
22 illustrated by the pink goal posts, bind LDL

1 particles and are internalized in vesicles. In the
2 acid environment of the vesicle, the LDL receptor
3 separates from the LDL particle and shuttles back
4 to the surface to bind another LDL particle while
5 the original LDL particle is broken down for reuse.
6 The LDL receptors are estimated to recycle
7 at least 100 times. When there are more LDL
8 receptors due to an increase in expression or
9 recycling, the cell clears LDL more efficiently,
10 and LDL levels are lower.
11 Statins also work by increasing LDL receptor
12 levels, although the mechanism is through
13 increasing the transcription of the LDL receptor
14 rather than promoting recycling.
15 When PCSK9 is present, it binds to the LDL
16 receptor. When the LDL receptor binds an LDL
17 particle and is internalized in a vesicle, the
18 PCSK9 roots the receptor to the lysosome for
19 degradation, blocking recycling and leading to less
20 LDL receptors and higher plasma LDL.
21 When evolocumab is administered, it binds to
22 PCSK9 in the bloodstream. The site of binding

1 sterically impairs the ability of PCSK9 to bind to
2 the LDL receptor. Without bound PCSK9, the LDL
3 receptor is free to recycle, and there are more
4 cell surface receptors, and LDL is cleared more
5 rapidly.
6 PCSK9 monoclonal antibodies are a great
7 example of how genetic validation can accelerate
8 the speed at which new therapies can be brought to
9 patients. The first genetic research demonstrating
10 PCSK9's role in LDL regulation and that PCSK9
11 mutations could cause premature cardiovascular
12 disease was published in 2003. Data that showed
13 that other mutations are protective came in early
14 2006.
15 In the same year, Amgen published the
16 crystal structure of PCSK9, elucidating the binding
17 site for the LDL receptor, and produced PCSK9
18 blocking antibodies. Clinical development started
19 with evolocumab in 2009, and within six years, in
20 2015, evolocumab received a positive opinion from
21 the CHMP in Europe.
22 During the rest of our presentation, we will

1 show you that LDL cholesterol is a major modifiable
2 risk factor for cardiovascular disease and is one
3 of the best validated surrogates in medicine.
4 Although we do have effective therapies available,
5 they are often insufficient to adequately control
6 LDL cholesterol.
7 Our large global clinical program has
8 demonstrated consistent and significant reduction
9 in LDL with favorable changes in other lipid
10 parameters. Safety and tolerability are favorable,
11 and no significant safety issues have been
12 demonstrated. This includes in subjects with very
13 low LDL.
14 There is a large, fully enrolled outcomes
15 study that is ongoing in 27 and a half thousand
16 patients. We have a robust clinical program and
17 ongoing pharmacovigilance prior to the conclusion
18 of this cardiovascular outcomes trial. And
19 finally, we believe that the benefit risk
20 assessment for evolocumab is positive.
21 At this stage, I'm going to ask Dr. Marc
22 Sabatine to come to the podium.

1 **Applicant Presentation - Marc Sabatine**

2 DR. SABATINE: Good morning. My name is
3 Marc Sabatine. I'm a cardiologist at Brigham and
4 Women's Hospital and chair of the TIMI study group,
5 which is a cardiovascular clinical trials group.
6 I've been an active investigator in evolocumab
7 program for several years and am currently the
8 co-chair of the executive committee for the ongoing
9 cardiovascular outcomes trial that Dr. Scott
10 mentioned. In addition, the TIMI study group had
11 adjudicated all of the cardiovascular events in
12 evolocumab program.
13 So cardiovascular disease is a
14 well-established public health issue. It affects
15 approximately 80 million Americans. It is the top
16 cause of death in the United States. The annual
17 costs are estimated to be approximately
18 320 billion. And careful epidemiological studies
19 have established several risk factors for
20 cardiovascular disease, including, importantly for
21 today's discussion, LDL cholesterol.
22 Now, LDL has been validated as a modifiable

1 risk factor through over 30 years of research.
2 Trials with statins provided a large volume of data
3 regarding the relationship between LDL reduction
4 and reduction in cardiovascular events in a variety
5 of patient populations and across different
6 baseline LDL values.
7 Now, here on this X/Y scatter plot, each
8 statin trial is represented by a red square. Its
9 location on the X-axis represents the absolute
10 reduction in LDL in that trial, and its position on
11 the Y-axis represents the relative risk reduction
12 in cardiovascular events in that trial, and the
13 size of each symbol is proportional to the amount
14 of data from that trial.
15 So you can see that more LDL lowering
16 translates into more risk reduction. And from
17 these data, an analysis performed by the
18 Cholesterol Treatment Trialists Collaboration that
19 Dr. Smith alluded to earlier, shows that for each
20 millimole or close to 40 milligram per deciliter
21 reduction in LDL, there is roughly a 20 to
22 25 percent reduction in cardiovascular events.

1 Thus, the absolute clinical benefit from LDL
2 lowering will depend on two factors: the patient's
3 risk of CV events and the absolute decrease in the
4 LDL.
5 Now, very similar results were seen with
6 studies over decades with non-statin interventions
7 such as niacin, bile acid sequestrants, fibrates,
8 and even surgical approaches, all of which showed
9 that when LDL was appreciably lowered and there
10 were no off-target adverse effects on other lipid
11 fractions or other parameters, then there was a
12 corresponding risk reduction
13 Now, to be clear, this is true for resins,
14 fibrates and niacin, where there was a large
15 reduction in LDL, we saw a large reduction in CV
16 events.
17 There have been some more recent trials that
18 have had very small LDL reductions and
19 non-significant reductions in CV events. But these
20 trials were not adequately powered to test the LDL
21 hypothesis. In contrast, the IMPROVE-IT study was
22 adequately powered for the LDL reduction and showed

1 that further LDL reduction with a non-statin added
2 to a statin further reduces CV events.
3 In addition, natural differences in LDL
4 levels associated with genetic variants also
5 support the relationship between LDL and risk. And
6 here are data from over 300,000 individuals, again,
7 plotting on an X/Y scatter plot the impact of the
8 variant on LDL in the X- axis and the reduction on
9 CV events on the Y-axis.
10 We see data on nine different genetic
11 variants affecting LDL in six different genes,
12 including HMG CoA reductase in dark blue, which as
13 we know is the target of statins, and PCSK9 in
14 purple, the target of evolocumab. The relationship
15 between lifelong exposure to lower LDL and risk of
16 coronary heart disease was approximately log linear
17 and importantly was consistent regardless of the
18 gene.
19 Now, let's examine key groups of patients
20 whose needs are not being met by current therapies.
21 Let me start by saying that statins are extremely
22 effective drugs and have proven outcome benefits.

1 And so as a clinician, I consider them our first
2 and most important option for controlling LDL.
3 There are other therapies such as resins,
4 niacin and ezetimibe. Their impact has been more
5 limited to date because of modest efficacy or poor
6 tolerability. And despite these options then, many
7 patients are unable to attain therapeutic goals
8 because either, one, their LDL cannot be controlled
9 despite intensive therapy, and really, three sets
10 of patients fall into this group.
11 There are patients at high cardiovascular
12 risk in whom even intensive statin therapy cannot
13 get their LDL under good control. Then there are
14 patients with heterozygous familial
15 hypercholesterolemia, who due to their monogenetic
16 disorder, have very high levels of LDL and whom
17 statins help but are not sufficient. And then
18 there are patients with homozygous FH who have
19 extremely high levels of LDL despite all current
20 therapy.
21 Then the other bin are patients who can't
22 take a statin or can only tolerate a low dose due

1 to side effects or, uncommonly, patients in whom a
2 fully effective dose of a statin is not advisable
3 due to drug interactions, active liver disease,
4 inherited muscle disease, or other clinical
5 circumstances when statin therapy needs to be
6 stopped or the dose reduced.
7 So now I'll go into more detail for these
8 four groups. So let me start with the first group.
9 Approximately 18 million patients in the U.S. are
10 considered high risk by NCEP and are on lipid-
11 lowering therapy. Half have diabetes alone. Let
12 me drill down on LDL control in the half with overt
13 vascular disease.
14 The most recent data from NHANES show that
15 only about a quarter, shown in green, have an LDL
16 less than 70. About half, shown in yellow, are
17 between 70 and 100, a level many would now consider
18 suboptimal. And then another quarter, shown in
19 red, are worse still with LDL levels above 100.
20 I think virtually all clinicians would want
21 to improve the LDL control for any patient in that
22 group in red. Most of us would also want better

1 control for many of the patients in the group in
2 yellow. And now with the results of IMPROVE-IT,
3 some, myself included, would want better control
4 for very high-risk patients who are still at 70.
5 Now, the inability to get LDL under good
6 control is not just in large observational studies.
7 It is also seen even in the most optimize setting,
8 namely, in clinical trials.
9 Plotted on this slide is the proportion of
10 patients with an LDL that remains greater than 70
11 using different doses of either simvastatin plus
12 ezetimibe or atorvastatin. And as you can see at
13 the far right, despite the use of the highest dose
14 of atorvastatin, 80 milligrams daily, 64 percent of
15 patients did not get to goal. Even combination
16 therapy with ezetimibe and simvastatin 80, the dose
17 that is no longer recommended for new initiation,
18 left more than one-third of patients above
19 70 milligrams per deciliter.
20 Now, turning to familial
21 hypercholesterolemia, a disease characterized by
22 the inability to clear LDL, most often due to a

1 defect in the LDL receptor gene but also sometimes
2 mutations in ApoB or as you heard earlier, PCSK9
3 for gain of function, the prevalence of
4 heterozygous FH has been estimated to be between
5 one in 200 to 1 in 500 in the U.S. This makes it
6 the most common genetic disease in the U.S. and
7 roughly eight times as common as cystic fibrosis,
8 for example.
9 Now, patients with heterozygous FH have very
10 high LDL levels, typically between 190 and
11 350 milligrams per deciliter, and for that reason,
12 they cannot achieve a desired level of LDL even
13 with the most effective statins, and in many cases,
14 even with add-on ezetimibe.
15 As shown on the right, a contemporary study
16 evaluating LDL levels in Dutch FH patients showed
17 that despite extensive use of high- dose statin and
18 frequent add-on drugs, only about 20 percent were
19 able to get below an LDL of 100, and practically no
20 one reached below 70.
21 For this reason, cardiovascular disease is
22 accelerated due to the persistent high cholesterol

1 levels. The age of CAD onset can be in the 30s in
2 men and the 40s in women. The lifetime risk of
3 developing heart disease is close to 100 percent.
4 Now, levels of LDL are even higher in
5 patients with homozygous FH, the prevalence of
6 which is approximately one in a million, and many
7 individuals develop symptoms of CAD in their teens
8 or even sooner. Prior to the use of statins, the
9 median age of survival was less than 30 years.
10 Statins and other lipid-lowering therapies have
11 extended the median survival into the fourth
12 decade, as shown in the graph on the right. But
13 homozygous FH remains a pretty dismal disease for
14 people who suffer from it.
15 Then while many patients cannot achieve goal
16 even with the use of high-dose statins, then there
17 are patients who appear unable to tolerate statins
18 at all or can only tolerate low doses. The rates
19 have been low in clinical trials, but some of these
20 trials had active run-in phases, making it hard to
21 interpret.
22 A variety of studies looking at the

1 incidence of statin intolerance in real-world
2 practice from populations or healthcare systems
3 have identified a rate of somewhere between 5 and
4 15 percent of patients who appear unable to take
5 any dose of a statin.
6 Actually, a higher percentage may initially
7 come off their statin therapy, but rigorous
8 re-challenging can get about two-thirds of patients
9 back on some dose of a statin, although not
10 necessarily the optimal dose.
11 Data from the two Amgen studies in
12 statin-intolerant subjects show that 92 percent of
13 subjects had failed at least two statins, and close
14 to half have failed three or more. The problem for
15 these patients is that they have very high LDL
16 values with the average LDLs, shown here, between
17 180 and 200 milligrams per deciliter. Thus, these
18 patients are in need of some other type of potent
19 LDL reduction to reduce their cardiovascular risk.
20 Finally, I'm going to discuss two important
21 issues: what is the expected clinical benefit of
22 achieving lower LDL values in patients on PCSK9

1 inhibitors, and whether we would anticipate any
2 safety concerns from very low levels of LDL.
3 So let me start by showing the 4S trial,
4 which was mentioned earlier, which enrolled
5 patients with high LDL and known vascular disease.
6 I show the placebo and statin arms of the trial
7 with the open and filled circles, respectively.
8 The position on the X-axis is the achieved LDL, and
9 the position on the Y-axis is the coronary heart
10 disease event rate at five years.
11 Subsequent trials that enrolled patients
12 with so-called average LDL levels then also showed
13 reduced cardiovascular risk with LDL lowering from
14 those average levels. And then more recent trials
15 such as TNT in patients with stable ischemic heart
16 disease, and then IMPROVE-IT TIMI 22, and then
17 IMPROVE-IT in patients with ACS here shown in red,
18 continue to show that lower is better.
19 These studies have demonstrated a generally
20 linear relationship between event rates and on
21 treatment LDL over a wide range of LDL from 194
22 down to 54 milligrams per deciliter. And

1 importantly, there is no level of LDL that has been
2 studied below which further LDL reduction has not
3 shown benefit.
4 Now, let me go a little bit further in terms
5 of low LDL. This meta-analysis of statin studies
6 performed by the Cholesterol Treatment Trialists
7 Collaboration shows that the 22 percent relative
8 risk reduction per millimole of LDL reduction that
9 Dr. Smith mentioned earlier is true regardless of
10 how low the patient started, including patients who
11 started with values less than 77 milligrams per
12 deciliter.
13 In IMPROVE-IT, we see consistent benefit
14 even when dropping LDL from the mid-60s to the
15 mid-40s with excellent safety data over seven
16 years. And lastly, in the JUPITER study, even in
17 patients who started with an LDL less than or equal
18 to 60, in whom rosuvastatin cut the LDL
19 approximately in half to an average therefore of
20 less than or equal to 30, showed a consistent
21 clinical benefit.
22 Now, as we started to achieve lower levels

1 of LDL in some of our clinical trials, people
2 wondered whether it would be safe. And
3 fortunately, we have conducted many studies, such
4 as TNT, PROVE-IT TIMI 22, JUPITER and now
5 IMPROVE-IT, where patients have achieved very low
6 levels of LDL without major safety concerns
7 emerging.
8 This should not be that surprising as almost
9 all cells can synthesize their own cholesterol and
10 are not dependent on circulating sources of
11 cholesterol for proper metabolism and membrane
12 function.
13 Cholesterol that does enter the circulation
14 from the liver or the gut does not enter as LDL but
15 rather as VLDL or chylomicrons. These particles
16 are then remodeled through interaction with the
17 endothelium or the lipoproteins. LDL is the final
18 product, which is then removed from the circulation
19 by the liver.
20 The brain specifically does not depend on
21 intravascular sources of cholesterol. Lipoproteins
22 do not cross the blood brain barrier, and so

1 cholesterol necessary for proper function is
2 synthesized within the brain.
3 Then specifically in terms of PCSK9
4 inhibition, it does not affect cholesterol
5 production. Rather, it enhances cholesterol uptake
6 in the tissues, which results in clearance from the
7 bloodstream. And although few in number, data from
8 individuals who have two loss of function alleles
9 for PCSK9 show that they have no detectable PCSK9,
10 very low circulating LDL, and are healthy.
11 In PROVE-IT TIMI 22, there was no evidence
12 that achieving LDL levels below 40 milligrams per
13 deciliter, here the dark green bars, was associated
14 with any specific safety concerns.
15 So in summary, statins are clearly the drug
16 of choice for the management of dyslipidemia. They
17 have been extensively studied over several decades
18 and have a wealth of positive outcome data. Though
19 statins are effective and well tolerated, there
20 remain key groups of patients -- and I list them
21 here on this slide -- who still require an
22 additional option for lipid lowering that is both

1 highly effective and safe because either their
2 clinical risk is high, their LDL remains high, or
3 both.
4 LDL is a proven modifiable risk factor for
5 cardiovascular event reduction. So far, there is
6 no level of LDL that has been studied below which
7 further LDL reduction has not shown benefit.
8 Specifically supporting the concept that LDL
9 reduction with PCSK9 inhibition should likewise
10 translate into a reduction in CV events are three
11 points. First, the mechanism of action, namely,
12 up-regulating the LDL receptor is the same as for
13 statins.
14 Secondly, looking at the genetics,
15 individuals who carry a loss of function variant in
16 the PCSK9 gene have a lower risk of cardiovascular
17 events. And the third as we've published -- and as
18 you'll see in a later presentation -- the
19 preliminary data on the effect of evolocumab on CV
20 outcomes is very encouraging.
21 Lastly, there are no substantiated major
22 safety risks from achieving very low levels of LDL

1 with this therapy that would offset the anticipated
2 benefit on hard cardiovascular outcomes.
3 So thank you very much for your attention.
4 I'd like to ask Dr. Scott Wasserman to come to the
5 podium.
6 **Applicant Presentation - Scott Wasserman**
7 DR. WASSERMAN: Thank you, Dr. Sabatine
8 My name is Scott Wasserman. I am a
9 cardiologist and a therapeutic area lead for
10 cardiovascular and metabolic at Amgen and will be
11 presenting the evolocumab program, efficacy, and
12 safety. I'll begin with our phase 3 dose-selection
13 rationale, and then I will discuss our development
14 program.
15 Shown here is the percent change in PCSK9
16 after 420 milligrams of subcutaneous evolocumab.
17 There is a rapid decline of PCSK9 to almost
18 undetectable levels within 4 hours, and this level
19 of suppression is maintained for 2 weeks.
20 Continued PCSK9 production by the liver and
21 typical monoclonal antibody elimination pathways
22 get rid of unbound evolocumab and return PCSK9 to

1 baseline. The reduction of PCSK9 is followed by a
2 reduction in LDL. As PCSK9 returns to baseline,
3 LDL follows. Because of this U-shaped response,
4 average LDL reduction gives a more accurate picture
5 of what is happening than looking at a single point
6 in time.
7 Here we show the relationship between PCSK9
8 inhibition and the percent reduction in LDL based
9 on modeling from our phase 1 dose-ranging studies.
10 When a dose of 21 milligrams is given every
11 2 weeks, you can see on the left that PCSK9 is
12 lowered by about 50 to 60 percent after each dose,
13 but there is a return to baseline by the end of the
14 dosing interval.
15 On the right, LDL declines with each dose
16 until steady state is reached around 8 weeks. Note
17 that there is considerable variability in
18 peak-trough levels.
19 With the higher dose of 70 milligrams every
20 2 weeks, PCSK9 is reduced by almost 100 percent and
21 nearly returns to baseline. LDL on the right is
22 reduced to lower levels and achieves steady state

1 faster. However, even with 70 milligrams, there is
2 considerable peak-trough variability or
3 fluctuations in LDL.
4 With the 140 milligram dose every 2 weeks,
5 there is prolonged, near complete suppression of
6 PCSK9 with minimal return to baseline. LDL levels
7 over the dosing interval are stable and effectively
8 reduced. Peak trough is minimized.
9 Now, turning to monthly dosing,
10 280 milligrams is insufficient to suppress PCSK9
11 for 4 weeks. With PCSK9 returning to baseline,
12 there is considerable recovery of LDL and marked
13 peak-trough variability.
14 420 milligrams monthly maintains over
15 40 percent suppression of PCSK9 for the full month,
16 and therefore, the LDL levels also remain more
17 stable with little peak-trough variability.
18 To provide additional insight into our
19 phase 3 dose selection, here is an integrated
20 analysis of our phase 2 pharmacokinetic/
21 pharmacodynamic substudy. On the left is mean LDL
22 over time for patients given evolocumab every

1 2 weeks compared to placebo. Monthly data are on
2 the right. LDL was assessed weekly, and arrows
3 show when evolocumab was administered.
4 Overall, 140 milligrams every 2 weeks and
5 420 milligrams monthly provide sufficient PCSK9
6 suppression to result in effective, sustained LDL
7 lowering with minimal variability. There is no
8 clinically meaningful difference in LDL reduction
9 between these two doses.
10 In addition, these doses provide an average
11 of 20 percent and 7 percent more LDL reduction
12 compared to 70 milligrams every 2 weeks and
13 280 milligrams monthly respectively.
14 We chose to bring forward a single dose for
15 each dosing interval, 140 milligrams for every
16 2 weeks and 420 milligrams monthly. These were the
17 most effective doses. They had similar efficacy
18 with the least inter-patient variability as
19 evidenced by the smaller standard deviations and
20 provided stable reduction with the least
21 peak-trough variability throughout the dosing
22 interval. Importantly, adverse events were no more

1 common at these doses than lower doses, placebo, or
2 ezetimibe.
3 Treatment with a lower, less effective dose
4 results in higher LDL, and we anticipate that this
5 will potentially result in more cardiovascular
6 events without improved safety.
7 Now, let's turn to our clinical program.
8 The clinical program is made up of 26 studies.
9 There were two biopharmaceutic studies and 8
10 clinical pharmacology studies. These were followed
11 by 16 phase 2 and 3 trials.
12 The phase 2 and 3 trials are shown here. On
13 the left are the indications for primary
14 hyperlipidemia and mixed dyslipidemia and
15 homozygous FH. Along the top, we note our initial
16 studies and open label extensions. Phase 2 studies
17 are in blue, and phase 3 are in orange. All the
18 phase 2 studies rolled into the blue open label
19 extension, and all the phase 3 studies rolled into
20 the orange open label extension.
21 For primary hyperlipidemia and mixed
22 dyslipidemia, we evaluated 4 patient populations

1 from top to bottom: heterozygous FH, combination
2 therapy with statins, monotherapy, and statin
3 intolerance. These populations were studied in
4 14 trials across approximately 6,000 subjects.
5 Of these, there are six key studies that we
6 will discuss in more detail as we review our
7 efficacy results. Studies 117, 115, 114 and 116
8 were 12-week studies, while study 109 was a
9 long-term 52-week study and study 110 was the open
10 label phase 2 extension, which shows our longest
11 exposure for evolocumab.
12 The other eight trials include four phase 2
13 dose ranging studies, a phase 2 study in Japanese
14 subjects, 2 phase 3 device studies, and the phase 3
15 open-label extension. These studies provide
16 additional supportive data.
17 Now, turning to homozygous FH indication, we
18 performed two phase 2/3 studies. Study 223
19 included a phase 2 pilot and a phase 3
20 double-blind, randomized placebo-controlled trial.
21 Study 271 is a long-term open label study that
22 enrolled subjects from study 233 as well as de novo

1 subjects.

2 I'll now turn to the study designs for our

3 six key primary hyperlipidemia and mixed

4 dyslipidemia trials. We conducted 4 12-week LDL

5 reduction studies in phase 3. You can see the four

6 populations near the top.

7 Heterozygous FH, subjects at varying levels

8 of cardiovascular risk to reflect the populations

9 that might benefit from additional effective LDL

10 reduction who are randomized to the three most

11 common statins at high or moderate intensity;

12 Subjects with a Framingham risk of

13 10 percent or less to allow ethical use of no

14 statin in a placebo-control and importantly,

15 enrolled to provide robust safety data in the

16 absence of potential confounding from statins or

17 statin intolerance;

18 And lastly, subjects intolerant to two or

19 more statins who are identified with a pragmatic

20 definition to resemble the kinds of patients

21 clinicians encounter.

22 LDL inclusion ranged from at least 80 to

1 100 milligrams per deciliter. Background
2 lipid-lowering therapy ranged from diet alone in
3 monotherapy study 114 to high or moderate intensity
4 statin therapy with or without ezetimibe in
5 studies 117 and 115.
6 All studies evaluated 140 milligrams every
7 2 weeks and 420 milligrams monthly of evolocumab
8 compared to placebo injections. In addition,
9 studies 115, 114 and 116 all had double blind
10 comparisons against ezetimibe.
11 Our key long-term studies looked at two
12 populations, subjects with a range of
13 cardiovascular risk on background lipid-lowering
14 therapy and the phase 2 open label extension. LDL
15 inclusion for the studies was at least 75 and
16 85 milligrams per deciliter.
17 Background lipid-lowering therapy ranged
18 from diet alone to atorvastatin 80 milligrams with
19 ezetimibe optimized by NCEP risk in study 109 and
20 standard of care in study 110. Study 109 compared
21 monthly 420 milligrams evolocumab to placebo
22 injections for 52 weeks. Study 110 compared

1 evolocumab on top of standard of care to standard
2 of care for year 1, after which all subjects
3 received evolocumab for up to an additional
4 4 years.
5 Now, turning to efficacy endpoints. In
6 phase 3, we chose a co-primary efficacy endpoint.
7 First, the average of the percent change in LDL
8 from baseline at weeks 10 and 12 to better describe
9 the effect on LDL over time; and second, the
10 percent change in LDL from baseline at week 12. We
11 took a similar approach with other lipid parameters
12 known to associate with cardiovascular risk as co-
13 secondary endpoints.
14 The week 10 and 12 and the week 12 results
15 are comparable, and thus, throughout this
16 presentation, we will focus on the week 10 and 12
17 results.
18 So turning to the demographics and
19 disposition for these trials, the clinical program
20 enrolled a representative population of subjects
21 that could need additional lipid-lowering therapy.
22 Of note, approximately half of the subjects were

1 female. Ages were 50 to 60 years, and while the
2 population was predominantly white, up to 8 percent
3 black or African-American, up to 19 percent Asian,
4 and up to 11 percent Hispanic or Latino were
5 enrolled. About half of the patients came from
6 North America.
7 Looking at baseline characteristics,
8 heterozygous FH subjects had LDL levels of nearly
9 160 milligrams per deciliter despite intensive use
10 of statins and ezetimibe. About half had high or
11 moderately high NCEP risk levels.
12 For monotherapy and open label trials, LDLs
13 were above 140 milligrams per deciliter. In
14 combination study 115 and long-term study 109,
15 baseline LDLs were roughly 100 milligrams per
16 deciliter in a setting of high and moderate
17 intensity statin therapy in all or nearly all
18 subjects respectively.
19 The unmet need in statin-intolerant patients
20 is clear with baseline LDL of roughly
21 190 milligrams per deciliter and over 70 percent
22 high or moderately high NCEP risk.

1 As you can see, in most of the phase 3
2 trials, 95 percent of subjects completed the
3 subcutaneous injections. The most common reasons
4 for discontinuing subcutaneous injections were
5 adverse events and subject request. Almost all
6 subjects completed the initial phase 3 studies or
7 rolled into the phase 3 open label extension.
8 The most common reason for discontinuing the
9 study were withdrawal of consent or loss to
10 follow-up. On average, about three-quarters of
11 patients in the initial phase 3 studies rolled into
12 the open label extension with the greatest number
13 of patients rolling over in the heterozygous FH,
14 statin intolerance, and combination therapy
15 studies.
16 Turning to efficacy. Here are the primary
17 results for our four phase 3 12-week double-blind,
18 randomized placebo- or ezetimibe-controlled trials.
19 The Y-axis is the mean percent change from baseline
20 in LDL at weeks 10 and 12. You can see that
21 evolocumab every 2 weeks in blue reduces LDL
22 compared to baseline by about 60 percent in all

1 four populations compared to a mild increase in LDL
2 for placebo-treated subjects in gray and about a 20
3 percent reduction with ezetimibe in yellow.
4 In addition, there is no clinically
5 meaningful difference in LDL reduction between the
6 every 2-week and monthly evolocumab doses. The
7 effect of evolocumab is consistent across these
8 four populations and with every 2-week and monthly
9 dosing.
10 To show the longest term data we have for
11 subjects on evolocumab, I draw your attention to
12 the results of the phase 2 open label study 110.
13 Along the X-axis is study weeks which begin with
14 the 12-week initial studies and then extended the
15 year 1 control period in the open label extension
16 and the year 2-plus all evolocumab period.
17 After the initial studies, subjects were
18 re-randomized 2 to 1 for the first year to
19 evolocumab plus standard of care or standard of
20 care alone, after which all subjects received
21 evolocumab. Subjects in blue, or newly randomized
22 in gray to evolocumab in year 1, rapidly have

1 comparable approximately 60 percent LDL reduction,
2 and this reduction is maintained out to week 112 of
3 the open label extension.
4 For subjects on evolocumab in the initial
5 study in green and randomized to standard of care
6 for year 1, you can see that their LDL returns to
7 baseline by approximately week 12 of year 1 without
8 evidence of rebound. When these patients are
9 restarted on evolocumab at the beginning of year 2,
10 they return to the same 60 percent reduction and
11 behave like patients on control, seen here yellow,
12 in the initial study in year 1 period.
13 To further evaluate the consistency of the
14 LDL reduction with evolocumab every 2 weeks and
15 monthly, we analyzed the difference in percent
16 change from baseline compared to placebo based on
17 age, gender, race, ethnicity, region, and glucose
18 tolerance status.
19 The data are presented in a forest plot
20 where the blue shading denotes a 55 t0 75 percent
21 LDL reduction. Evolocumab every 2 weeks or monthly
22 consistently reduced LDL by 55 to 75 percent

1 compared to placebo regardless of these factors.
2 We conducted a similar analysis based on
3 background therapy and cardiovascular risk by NCP
4 category. Again, evolocumab reduced LDL 55 to 75
5 percent compared to placebo irrespective of
6 background therapy or cardiovascular risk with no
7 clinically meaningful difference in the response
8 between every 2-week and monthly evolocumab.
9 Now, let's look at the effect of evolocumab
10 on the other pro and anti-atherogenic lipid
11 parameters. The colored bars within the four
12 graphs are the four individual phase 3 studies that
13 had a placebo comparator. In the top panel on your
14 left, evolocumab consistently reduced ApoB by 45 to
15 55 percent compared to placebo with no clinically
16 meaningful difference between every 2-week and
17 monthly evolocumab.
18 In the top panel on your right, we see a
19 consistent 25 to 35 percent reduction in Lp(a), or
20 lipoprotein(a), compared to placebo with no
21 clinically meaningful difference between the two
22 dosing regimens. This marked Lp(a) reduction

1 appears to be a hallmark of PCSK9 inhibition.
2 In the bottom panel on your left, as
3 anticipated, there was a more variable response for
4 VLDL that ranged from no response up to a
5 30 percent reduction compared to placebo. And in
6 the bottom panel on your right, there was a modest
7 5 to 9 percent increase in HDL compared to placebo,
8 and this is not unlike what you'd see with a
9 statin.
10 As shown in the briefing documents, similar
11 results were seen comparing evolocumab to
12 ezetimibe. In all, evolocumab consistently reduces
13 pro-atherogenic lipid parameters and modestly
14 increases anti-atherogenic lipid parameters.
15 Turning now to homozygous FH, the phase 3
16 part of study 233 with its 49 subjects was the
17 second largest double-blind placebo-controlled
18 trial ever conducted in homozygous FH. This study
19 enrolled 10 adolescents. Study 271 was an
20 open-label study that enrolled subjects from
21 study 233 as well as de novo subjects. Ninety-six
22 subjects were enrolled, including 31 on apheresis

1 and 13 adolescents. All subjects in these studies
2 were on stable lipid-lowering therapies.
3 Study 233 employed the monthly evolocumab
4 dose of 420 milligrams while study 271 permitted
5 up-titration of evolocumab from 420 milligrams
6 monthly to 420 milligrams every 2 weeks to ensure
7 adequate PCSK9 inhibition.
8 In phase 3 of study 233, about half the
9 subjects were female. Average age was 31 years,
10 and nearly half had coronary artery disease. All
11 subjects were on statins, and over 90 percent were
12 on ezetimibe.
13 Now, despite aggressive therapy, mean LDL
14 was approximately 350 milligrams per deciliter, and
15 PCSK9 was approximately 650 nanograms per
16 milliliter, which is about two times higher than in
17 the heterozygous and non-FH populations. A similar
18 patient profile was seen in study 271.
19 In study 233, evolocumab reduced LDL by
20 23 percent compared to baseline, while subjects on
21 placebo saw their LDL rise by 8 percent, resulting
22 in a difference of 31 percent.

1 This magnitude of percent reduction is less
2 than that observed in non-homozygous populations
3 and is likely due to lower LDL receptor
4 functionality as no response is seen in homozygotes
5 without LDL receptor function.
6 Nevertheless, given the markedly high LDL in
7 these patients, an absolute reduction of
8 94 milligrams per deciliter was achieved with
9 monthly evolocumab, and this is clinically
10 meaningful.
11 Across the two homozygous FH studies,
12 reductions in LDL, ApoB and Lp(a) were observed.
13 While the percent reductions in these parameters
14 was less than what was seen in non-homozygous FH,
15 the absolute reduction was greater in general.
16 Efficacy of evolocumab in homozygotes
17 compared to non-homozygotes in consistent to what
18 is seen with statins in these two populations.
19 Efficacy in apheresis in adolescents is similar to
20 the overall homozygous FH cohort.
21 Increasing the dose to 420 milligrams every
22 2 weeks resulted in an incremental statistically

1 significant 6 percent reduction in LDL or an
2 additional 20 to 30 milligrams per deciliter
3 absolute reduction in LDL compared to the
4 420-milligram monthly dose.
5 In summary, evolocumab 140 milligrams every
6 2 weeks and 420 milligrams monthly resulted in
7 consistent and clinically equivalent LDL reduction
8 of 55 to 75 percent compared to placebo and 35 to
9 45 compared to ezetimibe in primary hyperlipidemia
10 and mixed dyslipidemia subjects. The effect was
11 seen early and maintained with long-term therapy.
12 These two dosing regimens were effective in
13 all subgroups, including different background
14 therapies, age, gender, race, ethnicity, region,
15 and cardiovascular risk.
16 In homozygous FH, evolocumab reduced LDL by
17 30 percent compared to placebo with the
18 420-milligram every 2-week dose providing an
19 additional 6 percent reduction, which is akin to
20 doubling of a statin in a non-homozygous FH
21 patient.
22 Now, treatment with evolocumab in both of

1 these populations led to significant improvements
2 in other lipid parameters, including
3 lipoprotein(a).
4 Turning to safety, I will first describe the
5 safety database before discussing the results of
6 our evaluation. Our safety database was composed
7 of all the 16 phase 2 and 3 trials shown earlier
8 across all three time periods, including the
9 initial phase 2/3 periods in the center and the two
10 open-label extension periods on the right.
11 Analysis of the initial period is composed
12 of the pooled data from the 12 studies, which were
13 all double blind, placebo and/or active controlled
14 and ranged from 8 to 52 weeks in duration.
15 The year 1 control period represents the
16 first year of the open-label studies in which
17 subjects were re-randomized from their initial
18 studies in a 2 to 1 fashion to either evolocumab
19 plus standard of care or standard of care alone.
20 And lastly, after the first year, all subjects
21 received evolocumab for up to 3 to 5 years in
22 total.

1 We will focus our safety discussion on the
2 data from the initial studies and the year 1 period
3 of the open label extensions, both of which have
4 control arms. Safety in our two homozygous FH
5 studies was evaluated separately based on the rapid
6 and severe nature of their atherosclerotic disease.
7 Now, let's turn to safety in primary
8 hyperlipidemia and mixed dyslipidemia. Across our
9 phase 2 and 3 program, a total of 6,026 unique
10 individuals were enrolled. At the time of our BLA
11 submission, this data set encompassed 4,427
12 patient-years of evolocumab exposure and 1,797
13 subjects with 12 months or more of evolocumab
14 treatment.
15 The 120-day safety updated increased the
16 patient-years of evolocumab exposure to 5,246, the
17 number reaching at least 12 months of evolocumab
18 treatment, to 2,495, and treatment now extending
19 beyond 3 years.
20 Of the 6,026 subjects eligible to
21 participate in the open label extensions, 4,445 or
22 74 percent enrolled. Of the 26 percent that did

1 not enroll, the majority indicated that they would
2 not participate in the open-label extensions due to
3 personal reasons or the level of commitment
4 required.
5 To understand the generalizability of the
6 subjects enrolling into the open label extensions,
7 we evaluated the baseline characteristics of these
8 patients compared with those not participating in
9 the open-label extensions. These two populations
10 are generally similar with the caveat that the
11 open-label patients had slightly higher LDL and
12 higher cardiovascular risk.
13 In the safety data presented in our BLA, the
14 overall incidence of adverse events were similar
15 between evolocumab and comparator in the initial
16 and year 1 control periods. Most of the events
17 were grade 1 or 2, which is mild to moderate in
18 severity. The incidence of serious adverse events
19 was also similar between evolocumab and comparator.
20 The increase in incidence of serious adverse
21 events in year 1 compared to the initial studies is
22 consistent with an approximately 2.5-fold increase

1 in the duration of exposure.
2 Overall, the rate of adverse events leading
3 to discontinuation remained at approximately
4 2 percent throughout regardless of the treatment
5 period. The rate of fatalities was low throughout
6 and not higher in subjects treated with evolocumab.
7 We defined potentially drug-related adverse
8 events as those that were reported in more than
9 2 percent of subjects in the any evolocumab group
10 and more than in any control in the initial
11 studies. These adverse reactions were
12 nasopharyngitis, upper respiratory tract infection,
13 back pain, arthralgia, influenza, and nausea. Most
14 were mild to moderate and did not lead to
15 discontinuation of therapy.
16 Additional adverse reactions identified
17 based on medical review of search strategies and
18 individual events were injection site reactions,
19 rash, and urticaria. Again, most were mild to
20 moderate.
21 The most common serious adverse events in
22 evolocumab-treated subjects are shown here. Note

1 that this table includes all serious events,
2 including cardiovascular events regardless of
3 adjudication. Reported serious adverse events were
4 consistent with what is expected in the target
5 population.
6 No serious adverse event was reported in
7 1 percent or more of subjects in any treatment
8 group for any of the time periods. This evaluation
9 did not change with the 120-day safety update.
10 For the remaining safety discussion, we will
11 focus on the 120-day safety update data, which
12 provides an additional three months of exposure to
13 aid in the evaluation of cardiovascular events,
14 including mortality and events of interest.
15 Cardiovascular events were adjudicated based
16 on Clinical Data Interchange Standards Consortium,
17 or CDISC, definitions by the TIMI clinical events
18 committee that was blinded to treatment assignment
19 and lipid values.
20 Potential endpoint events were identified
21 and submitted to the clinical events committee via
22 case report forms. Sites were also queried about

1 potential events based on a regular review of the
2 adverse events.
3 In the initial period with a median exposure
4 of approximately 3 months, there were 34 positively
5 adjudicated cardiovascular events. No appreciable
6 effect on cardiovascular events was observed. In
7 the year 1 control period with a median exposure of
8 approximately 10 months, there were 52 additional
9 positively adjudicated cardiovascular events.
10 With long-term treatment, a lower incidence
11 of major cardiovascular events was observed in
12 subjects treated with evolocumab plus standard of
13 care versus standard of care. As the exposure and
14 number of cardiovascular events accumulated in the
15 year 1 control period, the data showed a reduction
16 in the cumulative incidence and relative risk of
17 all positively adjudicated events with evolocumab
18 plus standard of care as compared to standard of
19 care. The observed hazard ratio was 0.5 with the
20 upper bound of the 95 percent confidence interval
21 less than 1.
22 While these data are encouraging, the median

1 exposure in this analysis was approximately
2 10 months, and the number of cardiovascular events
3 was 52.
4 The definitive cardiovascular outcomes
5 study 118, or FOURIER, is fully enrolled with
6 approximately 27,500 subjects, and results are
7 anticipated no later than 2017.
8 A total of 19 deaths were reported of which
9 12 were cardiovascular and 7 were
10 non-cardiovascular. The etiologies of death are
11 not unexpected for this population. The subject
12 incidence of all-cause mortality was low and not
13 higher in subjects treated with evolocumab.
14 Events of interest reported with other
15 lipid-lowering therapies were analyzed by
16 standardized search strategies and laboratory
17 evaluations. The incidence of potential muscle
18 events by search strategy was about 5 percent in
19 each treatment period and similar between treatment
20 groups.
21 Elevations of creatine kinase greater than
22 5 times the upper limit of normal occurred

1 infrequently, and the subject incidence were
2 similar between treatment groups in the initial and
3 year 1 control periods.
4 The subject incidence of potential hepatic
5 disorder events by a search strategy and
6 transaminase elevations was low in each treatment
7 period and similar between treatment groups. There
8 were no cases of drug-induced liver injury assessed
9 to be associated with evolocumab use.
10 The incidence of new onset proteinuria by
11 urine dipstick was similar between treatment groups
12 in the initial and year 1 control periods.
13 We will now turn to our assessment of new
14 onset diabetes and neurocognitive events, two
15 events of interest recently reported with statins.
16 New onset diabetes was defined as having two
17 fasting glucoses greater than or equal to 126
18 milligrams per deciliter, a hemoglobin A1c greater
19 than or equal to 6.5 percent, diabetic adverse
20 events, or initiation of anti-diabetic medication
21 in a non-diabetic subject at baseline. The
22 incidence of new onset diabetes was low and

1 generally similar between treatment groups.
2 To further evaluate at-risk subjects at high
3 risk of developing diabetes, the non-diabetic
4 population was divided into those with normal
5 glycemia or those with impaired fasting glucose.
6 As expected, the incidence of new onset diabetes
7 was higher in those with impaired fasting glucose.
8 The incidence was generally similar between
9 the treatment groups. However, there was a small
10 imbalance with evolocumab in subjects with impaired
11 fasting glucose.
12 We also evaluated the incidence of impaired
13 fasting glucose in subjects with normal glycemia at
14 baseline. New onset impaired fasting glucose was
15 defined as two or more consecutive fasting blood
16 glucoses greater than 100 milligrams per deciliter
17 but less than 126 milligrams per deciliter.
18 The incidences were generally similar
19 between treatment groups. However, the incidence
20 of new onset impaired fasting glucose with
21 evolocumab was higher in the initial studies and
22 lower in the year 1 control period.

1 These figures show the long-term treatment
2 with evolocumab did not affect hemoglobin A1c or
3 fasting glucose. Shown here is hemoglobin A1c in
4 the top two figures and fasting glucose in the
5 bottom figures. Long-term treatment with
6 evolocumab plus standard of care in subjects with
7 normal glycemia or impaired fasting glucose, shown
8 in blue, had no effect on hemoglobin and A1c or
9 fasting glucose compared to subjects who received
10 standard of care shown in orange.
11 Similar results were seen in subgroups of
12 subjects with type 2 diabetes, metabolic syndrome,
13 or neither at baseline.
14 While this data set does not suggest a
15 definitive safety signal, it cannot be excluded.
16 We will continue to monitor this in the ongoing
17 program in the cardiovascular outcomes study 118.
18 So now turning to cognition, we performed an
19 assessment of neurocognitive events using a high
20 level group term search strategy that includes
21 terms such as confusion, memory impairment, and
22 dementia. The overall number of neurocognitive

1 adverse events was small. The incidence of
2 neurocognitive events with evolocumab was lower in
3 the initial studies and higher in the year 1
4 control period versus comparator.
5 Most neurocognitive adverse events were mild
6 and non-serious. There were two serious adverse
7 events, both in evolocumab-treated subjects. An
8 event of mild delirium in setting of a prolonged
9 hospitalization, traffic accident, and alcohol
10 withdrawal in the initial study and an event of
11 severe transient global amnesia in the setting of a
12 migraine in the year 1 control period that resolved
13 spontaneously while evolocumab was continued.
14 Overall, the number of neurocognitive
15 adverse events leading to discontinuation was low,
16 and among subjects that continued the
17 investigational product, many of these events
18 resolved spontaneously.
19 The most frequent adverse event preferred
20 terms were memory impairment and amnesia. Review
21 of the individual cases did not identify a pattern
22 related to time, to onset or outcome such as

1 worsening, improvement, or resolution, and this was
2 regardless of whether evolocumab or a comparator
3 were continued. As will be discussed later, there
4 was no relationship between low or very low LDL to
5 these events.
6 We analyzed hypersensitivity adverse events
7 using the MedDRA query search strategy. Overall,
8 the incidence of hypersensitivity adverse events
9 was low and somewhat higher in evolocumab subjects.
10 Most of the adverse events in both groups were
11 dermatitis, eczema, and rashes and were mild to
12 moderate.
13 Serious hypersensitivity adverse events of
14 contrast media allergy were reported in two
15 subjects. Anaphylaxis to penicillin and/or ACE
16 inhibitor use was reported in one subject, and one
17 subject experienced angioedema associated with IV
18 iron administration. Of note, there were 5
19 non-serious adverse events of angioedema, and all
20 had alternative etiologies.
21 We used validated assays to detect
22 anti-evolocumab antibodies in each clinical study.

1 The assay used in our program was based on the
2 ability of anti-drug antibodies to bridge two drug
3 molecules and was not isotype specific.
4 In the integrated phase 2 and phase 3
5 primary hyperlipidemia and mixed dyslipidemia
6 studies, the overall incidence of anti-evolocumab
7 binding antibody development was 0.3 after at least
8 one dose of evolocumab, and this date is as of the
9 120-day safety update. No anti-evolocumab
10 neutralizing antibodies were detected in any
11 subject.
12 In the few subjects who had binding
13 antibodies, there was no impact on
14 pharmacokinetics, efficacy, or safety.
15 To assess safety associated with low levels
16 of LDL, we performed thorough analyses of adverse
17 events using LDL cutoffs of less than 40 milligrams
18 per deciliter, shown here, and less than
19 25 milligrams per deciliter, which I'll show you in
20 a moment. Due to the small numbers of subjects
21 achieving these LDLs in the control groups,
22 meaningful comparisons between evolocumab and

1 control were not possible. However, it is possible
2 to compare the safety in evolocumab subjects
3 achieving low, or very low LDL, the column on the
4 left, with evolocumab and control subjects who did
5 not achieve these levels, the two columns on the
6 right.
7 It's important to recognize that these
8 analyses have limitations. These analyses were
9 determined by a post-baseline variable of
10 on-treatment LDL, so there's potential for
11 confounding, and these analyses do not incorporate
12 the timing of the relationship of the LDL to the
13 adverse event onset date.
14 In the year 1 control period, there were
15 approximately 1500 subjects in the evolocumab group
16 with LDL less than 40 milligrams per deciliter.
17 Subject incidence of adverse events, serious
18 adverse events, search strategies, and laboratory
19 abnormalities were similar to those subjects with
20 LDL of 40 milligrams per deciliter or greater on
21 evolocumab or standard of care.
22 Now, the rationale for the 25-milligram per

1 deciliter subgroup was that if there was a safety
2 issue due to low LDL, it would be most apparent in
3 this subset of subjects achieving the lowest LDL
4 levels.
5 The safety profile in the subset of over 750
6 subjects with LDL less than 25 milligrams per
7 deciliter did not identify clinically meaningful
8 differences in adverse events, serious adverse
9 events, search strategies, and laboratory
10 abnormalities.
11 In addition, we performed two sensitivity
12 analyses using more stringent definitions of low or
13 very low LDL. Results of both of these analyses
14 were consistent with the analysis I've shown here.
15 In summary, our analyses showed similar
16 safety profiles in subjects with low and very low
17 LDL on evolocumab compared to subjects with LDL
18 greater than or equal to 40 milligrams per
19 deciliter on evolocumab or a comparator.
20 So now turning to homozygous FH safety, the
21 99 subjects in this data set make this one of the
22 largest cohorts of homozygous FH subjects ever

1 studied in a clinical trial. These subjects
2 contribute to 63 patient-years of evolocumab
3 exposure. The 120-day safety updated increased the
4 patient year exposure to 88.
5 In study 233, adverse events were reported
6 in 36.4 percent of subjects in the evolocumab group
7 and 62.5 percent of subjects in the placebo group.
8 Common adverse events that were greater in the
9 evolocumab group than placebo were generally
10 similar to the primary hyperlipidemia and mixed
11 dyslipidemia studies.
12 In the open label extension study 271,
13 adverse events were reported in 68 percent of
14 subjects. Common adverse events were again similar
15 to the non-homozygous FH population.
16 Overall, in the homozygous FH population,
17 the safety observations were consistent with
18 findings from the primary hyperlipidemia and mixed
19 dyslipidemia populations.
20 So in summary, of the approximately 6,000
21 subjects in the phase 2 and 3 program, nearly 5,000
22 received evolocumab, resulting in nearly 4,500

1 subject years of evolocumab exposure in the initial
2 BLA. The safety database encompasses an
3 appropriate patient population with approximately
4 75 percent being high to moderate NCP risk.
5 Additionally, approximately 75 percent of the
6 subjects were on statins, and of the subjects on
7 statins, approximately 39 percent were on high
8 intensity statins and 52 percent were on moderate
9 intensity statins.
10 The incidence of adverse events was similar
11 to comparator. Serious adverse events and adverse
12 events leading to investigational product
13 discontinuation were infrequent and similar to
14 comparator, demonstrating favorable tolerability.
15 Safety profile in the long-term studies was
16 consistent with the initial studies and within the
17 expected rate for the population. And importantly,
18 we identified no major safety risk in subjects with
19 low or very low LDL.
20 Anti-evolocumab binding antibodies are rare
21 and non-neutralizing. There was no effect of these
22 rare anti-drug antibodies on safety. The safety

1 profile on the homozygous FH populations was
2 generally consistent with the non-homozygous FH
3 population.
4 Now, I'd like to turn it over to Dr. Scott,
5 who will discuss the benefit/risk profile of
6 evolocumab.
7 **Applicant Presentation - Rob Scott**
8 DR. SCOTT: Thank you.
9 Let's turn now to discussing who might
10 benefit from access to evolocumab while reiterating
11 that statins are the first-line therapy for
12 lowering LDL and cardiovascular risk.
13 Firstly, we have patients whose LDL is too
14 high to be controlled with statins even with the
15 addition of other therapies. In patients who need
16 additional LDL lowering after statins, the next
17 most effective therapy is ezetimibe, which reduces
18 LDL by 20 percent. This is only sufficient for
19 patients who are already close to their therapeutic
20 goal. After statins and ezetimibe, there are no
21 well tolerated options for effective LDL lowering.
22 Secondly, we have patients who cannot

1 tolerate an effective dose of a statin or in whom
2 an effective dose may be inadvisable for other
3 reasons. For these patients, there are no
4 effective options beyond ezetimibe.
5 So how might evolocumab be used in clinical
6 practice? On the left of this figure are the
7 statin-intolerant patients from study 116.
8 Approximately 70 percent of these patients were
9 high or moderately high NCEP risk. Their LDL was
10 approximately 190. With ezetimibe, the most
11 effective alternative for these patients, their LDL
12 came down to 157. Evolocumab reduced their LDL to
13 under 90, an absolute reduction of 100 milligrams
14 per deciliter.
15 In the center, we have heterozygous FH
16 patients from study 117. A hundred percent of
17 these patients were on statins, of which the vast
18 majority were high intensity, and over 60 percent
19 were also on ezetimibe. Despite this therapy,
20 their LDL was 156. Evolocumab reduced their LDL to
21 66, an absolute reduction of 90 milligrams per
22 deciliter.

1 Lastly, in the panel on the right, we look
2 at the NCEP high-risk patients in study 109 on
3 maximal combination of atorvastatin 80 milligrams
4 and ezetimibe. These high-risk patients had an LDL
5 of 118. Evolocumab reduced their LDL to 51, an
6 absolute reduction of 67 milligrams per deciliter.
7 In these patients that require additional
8 LDL reduction after statins, evolocumab provides
9 meaningful benefit in terms of marked LDL
10 reduction.
11 We've seen from Dr. Wasserman's presentation
12 that the safety of evolocumab does not differ by
13 the cardiovascular risk of the patient. Similarly,
14 we've seen that the LDL lowering efficacy is also
15 not impacted by cardiovascular risk.
16 However, the benefit that we're seeking is
17 prevention of cardiovascular events, and it's
18 tempting to just assume that most events can be
19 avoided by treating the patients at the highest
20 risk. As I will demonstrate, this is only partly
21 true since the baseline LDL plays a prominent role
22 in the benefit equation.

1 Let us consider a group of patients with
2 differing risks for a cardiovascular event over the
3 next 10 years and also consider a range of
4 different LDL levels. The columns at the top have
5 different LDL levels before evolocumab therapy, and
6 the rows represent subjects with different 10-year
7 baseline risk.
8 I've selected 5 percent because this is a
9 group of subjects at low risk that are not
10 currently recommended for statin therapy; 7 and a
11 half percent because this patients are at moderate
12 risk in whom statins are recommended. Finally,
13 stable coronary disease in patients on an intensive
14 dose is represented by 15 percent, and 30 percent
15 could represent patients with ACS. These two
16 groups are considered high or very high risk.
17 Knowing that evolocumab reduces LDL by
18 around 60 percent regardless of baseline LDL or
19 cardiovascular risk, we can estimate the average
20 absolute LDL reduction varies from 42 milligram per
21 deciliter in the patients starting at 70 to 114
22 milligrams per deciliter in the patients starting

1 at 190.

2 We know from the CCTC that each millimole,

3 or roughly 40 milligrams of LDL reduction, is

4 anticipated to reduce risk for a future event by

5 roughly 22 percent. Taking the absolute LDL

6 reduction for each level of baseline LDL, we can

7 calculate what the expected reduction of absolute

8 risk is for each level of baseline risk,

9 recognizing that until we have proof that the LDL

10 hypothesis holds for evolocumab, this is just a

11 hypothetical risk reduction.

12 Please note that this calculation is

13 conservative for two reasons. Firstly, the

14 calculation is based on the relative risk reduction

15 associated with five years of treatment, whereas

16 the clinical trial data, the epidemiological data,

17 and the PCSK9 loss of function data all suggest

18 that this is likely to be higher after 10 years of

19 treatment.

20 Secondly, the graph is cut off at a baseline

21 LDL of 190 for simplicity, whereas we know that

22 there are patients above this level, including

1 50 percent of the patients in our 116 statin
2 intolerance study and numbers of patients in the
3 114 and 115 studies.
4 In the two examples given on this slide, we
5 show that for the lowest risk group, 5 percent, at
6 the lowest LDL level of 70, the absolute risk
7 reduction is about 1 percent over 10 years. This
8 is probably not the ideal target patient
9 population.
10 For the highest risk group, 30 percent at
11 the highest LDL of 190, the expected absolute risk
12 reduction is 19 percent, a very impressive number
13 which yields a number needed to treat of around
14 5 patients for 10 years.
15 Finally, we use this calculation to populate
16 the rest of the cells. In order to put these
17 numbers into perspective, I've ringed the 10-year
18 absolute risk reduction projected from increasing
19 from a moderate dose of statin, 10 milligrams of
20 atorvastatin in this case, in the TNT study to an
21 intensive statin, 80 milligrams of atorvastatin, in
22 patients with stable coronary disease.

1 The answer to the question of how much
2 theoretical risk reduction justifies using
3 evolocumab before we have definitive outcome data
4 may vary, but the purpose of this presentation is
5 to illustrate the interplay between risk and
6 starting LDL levels in determining benefit.
7 In the interests of clarity, I've drawn a
8 line between those people expected to experience
9 less benefit than was demonstrated in TNT at the
10 top and those that are likely to have the same or
11 greater benefit below.
12 This relationship suggests that even
13 patients with moderate risk but higher levels of
14 LDL of 160 and above will experience significant
15 benefit from evolocumab. Patients at high risk,
16 such as stable coronary artery disease patients or
17 those with acute coronary syndrome, can experience
18 considerable benefit from a baseline of
19 70 milligrams per deciliter, the lowest level that
20 will be randomized into our outcome study.
21 These calculations show that the likely
22 benefit of evolocumab cannot be estimated purely

1 from the baseline risk of the patient but also has
2 to take into account the greater risk reduction
3 accruing from the greater LDL reduction in those
4 patients with higher LDL. These data also
5 demonstrate why Amgen elected to study subjects
6 with lower risk but higher LDL in the evolocumab
7 phase 2 and phase 3 program.
8 Physicians need the flexibility to take into
9 account both the underlying cardiovascular risk and
10 LDL levels in assessing the benefit/risk balance of
11 evolocumab for the individual patients.
12 Although we've seen no major safety risks
13 with evolocumab use, including in subjects who
14 achieve very low LDL, we're continuing to conduct
15 extensive clinical trial surveillance to permit the
16 detection of potential unidentified safety issues.
17 The open-label extension studies currently
18 have approximately 4 and half thousand subjects and
19 will continue to generate data into 2016 and 2018
20 with the bulk of the data concluding in the 2018
21 time frame. This open-label data analysis will
22 complement the ongoing double blind placebo-

1 controlled trials and cover the time period while
2 these trials are ongoing and still blinded.
3 Importantly, our double-blind placebo-
4 controlled trials, anchored by the 27 and a half
5 thousand subject outcomes trial, study 118, are all
6 fully enrolled and are regularly monitored by our
7 program-wide data monitoring committee to ensure no
8 avoidable risk of harm to subjects participating in
9 these trials. Cardiovascular event adjudication
10 continues to be performed by the independent TIMI
11 events committee.
12 We will initiate study 295, an open-label
13 extension to study 118, to continue safety
14 monitoring beyond seven years. Comprehensive
15 pharmacovigilance includes signal detection in
16 ongoing studies using detailed questionnaires to
17 elicit important case information for analysis.
18 This will occur in the postmarketing setting as
19 well in evaluation of postmarketing reports.
20 Adverse events and periodic safety reports will be
21 provided to the FDA.
22 Access to various databases will serve as

1 additional signal detection and validation sources
2 as well as provide background rates in relevant
3 populations for evaluating potential safety
4 signals.
5 We're working closely with the FDA to ensure
6 appropriate product labeling, including
7 communication of safety risk, as well as providing
8 instructions for the use of the device.
9 Educational materials are planned to be provided to
10 healthcare practitioners and patients as well as
11 the call center to help support questions on the
12 appropriate administration of the product.
13 Our open- label extension studies and the 27
14 and a half thousand subject cardiovascular outcomes
15 trial will be robust sources for ongoing safety
16 assessment. Please note that there is over 25,000
17 years of patient experience in the cardiovascular
18 outcomes study already, and you may wonder why
19 we've elected to perform such a large study. And
20 the reason for that is that we have used very
21 conservative statistical assumptions, one of which
22 is a very generous allocation for potential

1 crossover by drop in and drop out.
2 Given the events related to neurocognitive
3 events, this trial also includes a prospective,
4 randomized double-blind, neurocognitive substudy in
5 approximately 2,000 subjects using a validated
6 instrument to evaluate the impact of evolocumab on
7 cognitive function.
8 Long-term safety evaluation will continue
9 beyond seven years in over 2,000 subjects in our
10 open label extension of study 118.
11 Controlled and open label studies in FH
12 patients over age 10 will provide efficacy and
13 safety data in the pediatric population.
14 Finally, a multinational observational study
15 evaluating pregnancy outcomes in FH patients
16 exposed to evolocumab will provide safety data
17 during pregnancy.
18 Despite all of the advances in
19 cardiovascular care, cardiovascular disease remains
20 the leading cause of death in the United States
21 with over 700,000 Americans having a heart attack
22 and approximately 400,000 dying from coronary heart

1 disease every year. LDL is a major modifiable risk
2 factor for cardiovascular disease. Available
3 therapies, while effective, are often not
4 sufficient to adequately control LDL.
5 In routine practice, over one-third of
6 patients with coronary artery disease do not
7 achieve desired levels of LDL, and this is
8 consistent with what is observed under the ideal
9 setting of clinical trials.
10 Evolocumab demonstrated a consistent and
11 significant reduction in LDL with favorable effects
12 on other lipid parameters. The adverse event
13 profile with evolocumab is similar to comparator
14 with no major safety issues identified, including
15 in subjects achieving very low LDL.
16 Our robust clinical program with a fully
17 enrolled cardiovascular outcomes trial and ongoing
18 comprehensive pharmacovigilance activities are
19 appropriately designed to identify potential
20 evolving safety issues.
21 Thus, in conclusion, it is the sponsor's
22 position that the benefit/risk of evolocumab is

1 favorable and can address the clear unmet medical
2 need for patients that need additional robust LDL
3 reduction after statins.
4 We look forward to working collaboratively
5 with the FDA and the medical community to make an
6 impact in the global epidemic on cardiovascular
7 disease. Thank you very much for your attention.
8 **Clarifying Questions**
9 DR. SMITH: Thank you to the sponsor. We
10 now have some time available for clarifying
11 questions from members of the panel. Again, I'd
12 like to emphasize that the purpose of this part of
13 the day is to focus on clarifying questions and not
14 discussion of the issues that we'll be talking
15 about later. And again, a reminder if you signal,
16 Philip Bautista will put you on the list and get to
17 you in order or later today if we run out of time.
18 So the first question, Dr. Hiatt.
19 DR. HIATT: Thank you. I have a question
20 for Dr. Sabatine, and if you could put up slide 20
21 to address the question. First, I want to thank
22 you for your presentation. It was elegant, and I

1 think it helped frame the issue today, which is
2 we're being asked to consider approving a drug
3 based on LDL cholesterol as an approvable surrogate
4 in the absence of clinical outcome data with this
5 drug.
6 I'd also like to mention that this question
7 came up in a similar context about 10 years ago
8 when I was participating in the cardiorenal
9 advisory committee around blood pressure drugs.
10 And the question was similar in that there are a
11 number of different classes of blood pressure drugs
12 that lower blood pressure by different mechanisms
13 of action, but the issue was whether lowering blood
14 pressure per se, agnostic to the type of drug
15 class, would have cardiovascular benefit.
16 So the question comes to us today in a way
17 that I think we have good knowledge and certainty
18 from meta-analyses that statin drugs lower LDL
19 cholesterol and have a direct relationship in that
20 lowering to clinical benefit.
21 On this graph, you show not just cholesterol
22 drugs but other forms of lipid-lowering therapies,

1 including lifestyle, ilio bypass, and a variety of
2 drug classes.
3 Now, my question to you is not to debate
4 this but to ask you to help us to inform our
5 thinking a bit further about whether all other
6 non-statin drugs classes really show a similar
7 benefit to statin drug classes.
8 I'd highlight a couple things. One is
9 niacin, which is on the lower-left corner of that
10 figure. And HPS2-THRIVE was a very large outcome
11 trial, almost 27,000 patients, almost four years of
12 follow-up. And it had a net lowering of LDL
13 cholesterol of 10 milligrams per deciliter, which
14 is not a lot, but it did lower LDL cholesterol.
15 Now, if niacin was a new molecular entity
16 and we're asked to review that today under the
17 current circumstance, we would say that it lowers
18 LDL cholesterol, must be beneficial. But as you
19 know, the hazard ratio for that trial was .96. It
20 was a non-statistical effect.
21 Now, you would say it falls on the line, I
22 guess, but I would like to ask you to clarify that

1 because in reality, it's a negative trial. So in
2 reality, if we're asked to -- with that information
3 to approve niacin for this indication with a
4 negative trial, we'd say it's negative. It didn't
5 help. The clinical benefit was not evident.
6 I also notice that CETP inhibitors are not
7 on this figure, and Dr. Smith in his earlier
8 comments noted that there was actually an increased
9 risk of all-cause mortality with at least one of
10 the drugs in that class.
11 So again, I think that there are a couple of
12 examples where the LDL surrogate hypothesis doesn't
13 hold up, and I want to ask you to clarify your
14 thoughts on this. Do you truly believe that in all
15 circumstances, for all forms of therapy, that
16 target LDL, no matter what your approach to
17 lowering LDL, that drug is, quote, "safe," do you
18 believe it retains a cardiovascular benefit?
19 DR. SABATINE: Well, thanks. It's a great
20 question for a very complex topic, and I'll try to
21 go through the different points that you raised.
22 So when I made that statement, I was careful

1 to point out that as long as it didn't have other
2 off-target effects, and I'll get back to that point
3 in a minute because it has to be part of the
4 calculus for sure.
5 With regard to the trials here -- and niacin
6 is a very good example. So in HPS2, as you
7 absolutely rightly pointed out, the delta in LDL
8 was about 10 milligrams per deciliter. Based on
9 CTT, you would expect that to translate into about
10 a 6 percent risk reduction, and they saw a
11 4 percent risk reduction. So in my mind, it's
12 really hard to distinguish whether that falls on
13 the line or not.
14 I think the point I was trying to convey was
15 that many of the more recent trials, where LDL has
16 essentially been forced down to a very low level,
17 and then you add on a therapy that has a very small
18 effect on LDL, isn't really a fair test of the LDL
19 hypothesis.
20 If you go back in time to other trials with
21 niacin like CDP, there, there was about a
22 26-milligram per deciliter difference, you would

1 expect that to translate into about a 15 percent
2 risk reduction, and they saw a 15 percent risk
3 reduction. So I think the more recent trials
4 aren't a proper test of the LDL hypothesis just
5 because the intervention is relatively modest.
6 Even in HPS2-THRIVE, if you look at some of
7 the subgroups, it was in general fairly consistent,
8 but one of the ones where it looked like there
9 tended to be more difference was on LDL. And those
10 who came in with higher LDLs therefore had a bigger
11 delta in LDL and a bigger risk reduction.
12 So in the subgroup that had the highest,
13 roughly, tertile of LDLs, the delta in LDL was
14 about 15, and the point estimate for the risk
15 reduction was 11 percent, a subgroup, but in my
16 mind, it flows along with this.
17 Then you rightly raise the point about what
18 about the CEPT inhibitors, so I don't have
19 torcetrapib because of the off-target effect. You
20 could say, well, why not have dalcetrapib, but that
21 doesn't affect LDL at all. So if we think on the
22 X-axis it's going to be at zero, then I'm not going

1 to expect under this paradigm it to have any
2 cardiovascular effect.
3 Then I think the broader question you raise
4 is, of course, you have to look at this in the
5 context of the mechanism, and I agree with you
6 100 percent for that. So for small molecules where
7 the mechanism for LDL -- maybe we understand, maybe
8 we don't, but there could be many pleiotropic
9 effects -- then I have greater concern that there
10 won't be something that's off target.
11 Conversely, I think for a monoclonal
12 antibody, it should be highly specific. Then the
13 mechanism of action for that monoclonal antibody is
14 ultimately to up regulate the LDL receptor, so
15 that's entirely analogous with statins. And then
16 we have the genetic data as a natural experiment,
17 that those people have the loss of function variant
18 do indeed have a greatly reduced risk of
19 cardiovascular disease.
20 So I think coupled with all that together,
21 then I have very high confidence, in particular,
22 for evolocumab. If you looked at other compounds,

1 you would have to, to your point, take into account
2 could there be off-target effects and what's the
3 likelihood. But I think for evolocumab, I have
4 much higher certainty that the -- or I anticipate
5 there to be a benefit that should really flow along
6 the lines of statins.
7 That's what we saw actually in the outcomes
8 trial, again, very small numbers, but still it
9 actually falls along that line.
10 DR. HIATT: So thank you, and I'll conclude.
11 I think the thing that we're wrestling with
12 yesterday and today is that we're left with
13 extrapolation, and your answer in part was
14 consistent with that. And I think that what we're
15 asking is do we need clinical evidence or not.
16 Clearly, the sponsor's made a commitment, but
17 that's really the heart of the struggle for me
18 today is trying to make -- whether that
19 extrapolation is true or not.
20 DR. SMITH: Dr. Burman.
21 DR. BURMAN: Thank you. Just points of
22 clarification for either Dr. Sabatine or

1 Dr. Wasserman. Number one, did you actually
2 measure LDL particle size and number in patients on
3 evolocumab? Did you measure CRP? And in slide 74,
4 could you give the exact numbers of individuals who
5 were not Caucasian?
6 DR. WASSERMAN: Yes. Let me deal with the
7 CRP and the slide 74, and then I'm going to
8 actually ask Dr. Rob Scott to deal with your
9 question on the particle size.
10 So in terms of CRP -- slide up -- we have
11 measured CRP, and as it appears to be somewhat
12 consistent with this mechanism of action, we have
13 not to date seen an effect. So this is our -- you
14 see study 109, which is our 52-week study and
15 study 114 which is our monotherapy study. And then
16 115 is a combination therapy, so everyone's on high
17 and moderate intensity statin, 116 statin
18 intolerant, and 117 is heterozygote where basically
19 everyone's on high and moderate intensity statin
20 with ezetimibe.
21 You can see that first and foremost, the
22 median CRPs are pretty normal. So with these

1 studies and the duration of studies, we did not see
2 an effect in terms of change. We also wouldn't
3 necessarily anticipate it.
4 In our ongoing cardiovascular outcomes
5 study, one of the ways that we enhance risk in that
6 is actually allowing for patients to have an
7 increased high sensitivity CRP. So I think that
8 that ongoing study will actually better address any
9 questions we have around PCSK9 inhibition with
10 evolocumab and CRP.
11 Then regarding 74, in the entire -- out of
12 the 6,000 patients that we had in the clinical
13 trial, 8 percent of that, so nearly 500, were
14 Asian. In terms of the African-American or black
15 subjects, it's 6 percent out of the 6,000, so a
16 little bit under 400. And then in terms of the
17 Hispanic and Latino, it was 5.4 percent, so it's a
18 little bit over 300 patients.
19 So that's why in general I'd say that
20 there's a little bit more variability around those
21 estimates.
22 DR. BURMAN: LDL particle size, please?

1 DR. WASSERMAN: Yes. Dr. Scott?
2 DR. SCOTT: Thank you. We did conduct an
3 analysis using both NMR and VEP, the vertical
4 analyzer, for some of our phase 2 and phase 1 data.
5 And what we saw there is pretty much what you would
6 expect when you lower LDL by 60 percent to
7 70 percent in those studies. We saw that particles
8 of all different sizes went down.
9 So I can't say that there was a particularly
10 selective response in terms of particle sizes,
11 which smaller or larger particles are going down,
12 but all different categories of particle sizes went
13 down pretty much as you would expect.
14 DR. SMITH: Dr. Sager.
15 DR. SAGER: In the homozygous FH group, you
16 studied 420 twice a week but also once a month.
17 Can you show us how many subjects were in those two
18 groups, and then the safety data between those two
19 different doses?
20 DR. WASSERMAN: Sure.
21 DR. SAGER: Then I have a second follow-up
22 or second question after that.

1 DR. WASSERMAN: So I would say in total,
2 there are about 100 patients. Slide up. So this
3 is our baseline demographics in our homozygous FH
4 study. So this is looking at the patients that
5 were either in 233 that rolled over or came into
6 271 de novo. All of these patients have homozygous
7 FH.
8 So you can see that in terms of patients
9 that have only been on monthly, there was 25, only
10 that have been on every 2 weeks, it's 28. And I do
11 want to note that the ones that are on every
12 2 weeks, I believe are all on apheresis. The ones
13 that went from QM and Q2W is, I believe, a mixture
14 of the two. Then in terms of up-titration from QM
15 to Q2W, it's a mixture as well.
16 Oh, it's hom on apheresis. Sorry. Excuse
17 me. It was a challenging study because we were
18 trying to ensure that patients with homozygous FH,
19 which I know you can appreciate, is a very severe
20 disease, had access and ability to enroll in a
21 clinical trial.
22 Then the next slide -- slide up -- so this

1 is our adverse event data in the homozygous FH
2 study according to the dose regimen. What you're
3 seeing on the left are just the patients that
4 stayed on monthly, and then you can see on the
5 patients on the right that went from monthly to
6 every 2 weeks.
7 Now, the caveat here is that none of these
8 patients are on apheresis, so it's -- we tried to
9 give you a sense of apples to apples in this case.
10 You can see that, in general, all adverse events
11 are similar. However, there does appear to be a
12 slightly higher risk of incidence of grade 2 events
13 and grade 3 and some serious adverse events.
14 Slide up. For the serious adverse events,
15 these are things I think that, in general -- for
16 those of the panelists that are familiar with these
17 patients, these are the common sequelae of FH. And
18 remember, the average age of these patients was
19 about 31.
20 So we saw two patients with aortic valve
21 disease, one with aortic stenosis, one just with
22 aortic valve disease. And then we had chest pain,

1 angina, coronary artery disease, and coronary
2 artery occlusion. In general, this is what you'd
3 expect in this population. We don't think that
4 it's a dose-related issue. We just think it's the
5 natural history of the disease.
6 DR. SAGER: Thank you. And then on
7 slide 97, you showed us a composite of cardiac
8 endpoints. I wonder if you had that just for MACE,
9 and if you could also, just out of interest -- pure
10 MACE, cardiovascular death, non-fatal stroke and
11 MI. And also, if you could just tell us the number
12 of patients who had unstable angina that required
13 hospitalization.
14 DR. WASSERMAN: So let me see.
15 DR. SAGER: So the same slide but using a
16 more typical MACE.
17 DR. WASSERMAN: Slide up. So this is what I
18 have for you right now. These are all of our
19 cardiovascular events in the year 1 control period.
20 You can see death at a 0.1 percent versus standard
21 of care, 0.33. All our coronary artery events,
22 0.71 versus 1.14. Cerebrovascular events at 0.12

1 on evolocumab, 0.56 on standard of care. And then
2 heart failure hospitalization, 0.3, 0.07.
3 I do want to note, Dr. Sager, that we show
4 this as a -- it's hypothesis generating. We as a
5 sponsor fully understand that it should be
6 hypothesis generating. This is not meant to be
7 definitive. It is a small number of events, and so
8 we can torture data. I just worry that we -- we
9 wanted to share it with you, but we want to make
10 sure it's very clear that this is hypothesis
11 generating.
12 DR. SAGER: Totally understand. Maybe after
13 lunch, you could just show us the same slide.
14 DR. WASSERMAN: I'll see what I can do.
15 DR. SAGER: Great. Thanks a lot.
16 DR. SMITH: So again to clarify,
17 specifically what would you like to see, just the
18 standard MACE, or are there other endpoints you'd
19 like to see assembled, if I understand?
20 DR. SAGER: The standard MACE assembled, and
21 I'm just curious to know what the unstable angina,
22 the resulting hospitalization numbers were.

1 DR. WASSERMAN: Slide up. The powers of the
2 Internet. These are adjudicated cardiovascular
3 events. This is actually from Dr. Sabatine's New
4 England Journal of Medicine article.
5 So in terms of MACE, you can see the
6 evolocumab group is about 0.95. The standard of
7 care group was 2.11. And then you asked around the
8 coronary vascularizations. So it was 15 in the
9 evolocumab group for 0.5 and then 17 in the
10 standard of care group at 1.1.
11 DR. SAGER: Thank you.
12 DR. WASSERMAN: You're welcome.
13 DR. SMITH: Dr. Nason.
14 DR. NASON: Thanks. One of my questions is
15 just largely to clarify your format of how you're
16 presenting adverse events. So for instance,
17 slide 120, which is the neurological -- sorry, I
18 had it opened and then I lost it -- neurological
19 adverse events, I noticed that the grade 1, 2 and 3
20 do not add to the all adverse events, and I think
21 that's true on some other ones, too.
22 So I just wanted to understand if all

1 adverse events were each patient is only counted
2 once, but then when it's broken down by grade, each
3 patient can be in multiple grades?
4 DR. WASSERMAN: That's correct. You've got
5 it.
6 DR. NASON: Okay. I almost wish to see it
7 both ways, to be able to see how many patients
8 also -- not just for this, but in general, when
9 there are multiple patients -- or when there are
10 single patients and there are multiple times, it
11 can be hard sometimes to tell necessarily what's
12 going on.
13 Then I guess the other question, which is
14 sort of also a more general question, is that on
15 many of your studies, you're reporting the mean
16 change, which is obviously very important on LDL
17 and even on the CV outcomes data when you have it.
18 But it's also interesting sometimes to know more
19 individual or more ranges of change. So for
20 instance, how many people go very low since the low
21 LDL is one of the concerns, or how many
22 people -- are there people it doesn't affect at

1 all, for instance, and that don't go down.
2 So some sense of the range of the responses
3 would be useful, and maybe even the percent that go
4 below 40 or 25 or whatever.
5 DR. WASSERMAN: So I'm hearing a few
6 questions there. One was you'd like to see the
7 number that go low, and then you also kind of
8 wanted to get a sense of the range and whether
9 there were any non-responders; is that --
10 DR. NASON: Yes. That was an example. I
11 don't know if -- it's more just the mean. Mean is
12 obviously very interesting, but it doesn't
13 necessarily --
14 DR. WASSERMAN: I'll do my best to help you.
15 So slide up. This is our prevalence of a low LDL.
16 What we used for this, this is our year 1 control,
17 so it's nearly 3,000 patients. We looked at it
18 three different ways.
19 So you see that there's any LDL below that
20 number, so it's less than 40, less than 25, less
21 than 15. Obviously, as you go down, there are
22 subgroups of the subgroups above; an LDL that's

1 below that number for at least two values; and then
2 having all the LDL values that we ever collected in
3 the clinical trial program on that individual
4 patient below that level.
5 So if you're interested -- are you
6 interested in a particular one that you wanted me
7 to focus on?
8 DR. NASON: No. You could grab the center,
9 two measurements below --
10 DR. WASSERMAN: Sure. So if we want to
11 focus on the less than 25, if you look at just
12 having one LDL less than 25, it's 26 percent. If
13 you have at least two, it's 9 percent. And then
14 for all of them, it's 5 percent.
15 If you're really concerned about very, very
16 low LDLs, less than 15, which is basically what you
17 see in patients that have homozygous PCSK9 loss of
18 function, you can see that there was 9 percent for
19 any one value that was below 15, 2 percent for at
20 least two values below that, and about 1 percent or
21 less than 1 percent that had all of them. So I
22 hope that gives you a sense of what it would look

1 like.

2 Slide up. So this is just to give you a

3 sense of how -- and you have to take this with a

4 grain of salt because these are two different

5 populations from two different trials. But we

6 wanted to be able to try to articulate what type of

7 response you might expect from evolocumab. And in

8 this case, these are patients that are all on

9 moderate or high intensity statins, so 39 percent

10 on moderate and I believe 52 percent -- 39 percent

11 on -- it's 44 percent and 50-something percent.

12 Sorry.

13 So this is the rosuvastatin 20 milligrams

14 from JUPITER. You can see kind of how the response

15 is, where there's a nice distribution above and

16 below 50 percent, and then for evolocumab, you can

17 see that the majority of the patients are below

18 50 percent. And I would say that all of these

19 patients except for a few of those, those

20 3 patients on the far right are less than

21 15 percent.

22 In general when we've explored those

1 patients that, quote, unquote, "don't respond,"
2 typically, they haven't been adherent to their
3 statin therapy or have not come in for their last
4 injection.
5 DR. SMITH: I'm aware that we have not made
6 it to everyone who had a question. We'll have an
7 opportunity for you to ask your questions later on
8 today, but we'll now take a 15-minute break.
9 Panel members, please remember there should
10 be no discussion of the meeting topic during the
11 break among yourselves or with any member of the
12 audience. And we will resume promptly at 10:30.
13 Thank you.
14 (Whereupon, at 10:15 a.m., a recess was
15 taken.)
16 DR. SMITH: So we'll now proceed with the
17 FDA presentations, and Dr. Craig, I guess you're
18 going to do that.
19 **FDA Presentation - Eileen Craig**
20 DR. CRAIG: Good morning, Chairman Smith,
21 members of the committee. My name is Eileen Craig,
22 and I will be presenting the division's perspective

1 on the evolocumab clinical development program.
2 I will begin with some background, then I
3 will move on to the clinical program, efficacy
4 finding, and some of our safety concerns.
5 As you've heard already this morning,
6 evolocumab is a human monoclonal immunoglobulin G2
7 antibody directed against PCSK9. Evolocumab binds
8 to PCSK9 and inhibits circulating PCSK9 from
9 binding to the low density lipoprotein receptor on
10 the liver cell surface. This action prevents
11 PCSK9-mediated LDL receptor degradation, which
12 leads to increases in LDL receptor and results in
13 decreases in serum LDL.
14 For hyperlipidemia, the proposed dose is
15 either 140 milligrams every 2 weeks or
16 420 milligrams once a month. For homozygous
17 familiar hypercholesterolemia, the proposed dose is
18 either 420 milligrams either once monthly or every
19 2 weeks. One single use prefilled syringe or a
20 single use prefilled auto injector delivers the
21 140-milligrams every 2-week dose, and 3 single-use
22 prefilled syringes or prefilled auto injectors

1 administered consecutively within 30 minutes
2 delivers the 420-milligram once a month dose.
3 As background, I'd like to discuss some of
4 the important regulatory discussions. The division
5 held an end of phase 2 meeting with the company in
6 July of 2012 to discuss the evolocumab development
7 program. Topics of discussion included, first,
8 given that statins are lipid-lowering drugs with
9 robust cardiovascular outcome data in an extensive
10 safety database, evolocumab monotherapy and
11 superiority to ezetimibe and statin claims would
12 likely require cardiovascular outcome trial data.
13 Second, we had concerns regarding only
14 taking two dosing regimens, the every 2-week and
15 every 4-week, into phase 3 when both dosing
16 regimens seemed to yield approximately the same
17 degree of LDL lowering. One of the reasons for
18 this is if chronic low LDL levels do present a
19 safety concern, there is no mechanism to
20 down-titrate the dose of evolocumab. The physician
21 would either have to discontinue evolocumab,
22 down-titrate the statin dose, or use an off label

1 and not studied dosing regimen for evolocumab.
2 As statins have a robust safety database and
3 positive cardiovascular outcome, which evolocumab
4 does not have, we do not believe that titrating the
5 dose of the statin is a preferable option.
6 Next, we expressed concerns with some of the
7 proposed study populations who may not be taking
8 the maximum tolerated dose of statin. The division
9 expected that placebo-controlled studies such as
10 protocol 115, which is combination with statins,
11 would enroll patients who are not at goal despite
12 taking the maximal tolerated dose of statin with or
13 without other lipid-modulating agents. And lastly,
14 that we prefer that the duration of the short-term
15 phase 3 studies be at least 24 weeks.
16 In a meeting to discuss the design of the
17 statin intolerance trials, we stated that based on
18 data from phase 2, from an efficacy perspective, we
19 believe that the statin-tolerant and
20 statin-intolerant populations would respond
21 similarly. We stated that focusing on the clinical
22 question of tolerability instead of efficacy should

1 influence the study design.
2 We again shared the division's draft
3 definition of statin intolerance, which includes
4 the inability to tolerate at least two statins of
5 which one statin is at the lowest starting daily
6 dose and involves symptoms that began or increased
7 during statin therapy and stopped when statin
8 therapy was discontinued.
9 The division's intent in developing such a
10 definition was to encourage consistency among
11 sponsors in exploring the concept of statin
12 intolerance in clinical trials. Thus equally
13 important to the definition itself, the division
14 recommended trial design elements as well,
15 including a blinded placebo run-in period and a
16 statin re-challenge arm.
17 Given that statins are the only
18 lipid-lowering drugs with positive cardiovascular
19 outcome data for multiple trials, as well as robust
20 long-term safety data, we felt it was important to
21 ensure a rigorous and trial tested definition of
22 statin intolerance.

1 Our concern is that without these
2 safeguards, patients with symptoms on statins that
3 are not, in fact, due to the statin or are not
4 decreased in a clinically meaningful manner, could
5 be inappropriately encouraged to switch over to a
6 therapy that has a much smaller safety database and
7 lacks cardiovascular outcome data.
8 We also stated that 12 weeks of evolocumab
9 is insufficient to describe tolerability. A
10 minimum of 24 weeks of evolocumab would be required
11 in a randomized double-blind controlled, parallel
12 group trial.
13 The applicant's proposed indication for
14 primary hyperlipidemia is outlined on this slide.
15 It focuses on the reduction of LDL and other lipid
16 parameter changes in combination with statins or
17 other lipid-lowering therapies and also as
18 monotherapy and combined with other lipid-lowering
19 therapies in patients who are statin intolerant or
20 for whom a statin is not clinically appropriate.
21 The applicant's proposed indication for HoFH
22 is outlined on this slide. It focuses on the

1 reduction of LDL and three other lipid parameters
2 in patients with HoFH who are 12 years or older.
3 Also listed are the drugs that are currently
4 approved for the reduction of LDL in HoFH
5 populations, which includes statins, statin
6 combinations with ezetimibe, ezetimibe, lomitapide,
7 and mipomersen.
8 The efficacy of evolocumab was assessed in
9 four double blind randomized placebo or ezetimibe
10 controlled phase 3 trials of 12 weeks' duration and
11 one 52-week placebo-controlled trial. The four
12 12-week trials evaluated evolocumab in four
13 different patient populations, trial 114, which is
14 monotherapy in a population at low CV risk, which
15 is defined as a 10-year Framingham risk score of 10
16 percent or less. Trial 115 is in combination with
17 statins; trial 116 is statin intolerance; and 117
18 is heterozygous familiar hypercholesterolemia.
19 For the statin combo trial 115, after this
20 screening period, eligible subjects were first
21 randomized to one of five open label statin
22 cohorts, which consisted of atorvastatin 10 or

1 80 milligrams, rosuvastatin 5 or 40 milligrams, or
2 simvastatin 40 milligrams for the lipid
3 stabilization period. Randomization into the
4 statin dose cohorts was stratified by entry statin
5 therapy such as no statin use versus non-intensive
6 statin use versus intensive statin use.
7 After the lipid stabilization period,
8 eligible subjects were randomized within each
9 statin dose cohort to evolocumab, placebo, or for
10 the atorvastatin cohorts only, ezetimibe.
11 This slide summarizes some of the key
12 inclusion and exclusion criteria for the four
13 phase 3 trials. In all four trials at screening,
14 participants had to have fasting triglycerides of
15 less than 400 milligrams per deciliter.
16 The entry criteria for LDL varied among the
17 four trials. In 114, the fasting LDL was between
18 100 and 190. In 115, subjects on intensive statin
19 therapy had a fasting LDL of greater than 80.
20 Subjects on non-intensive statin, fasting LDL was
21 greater than or equal to 100. And subjects not
22 taking a statin, fasting LDL was greater than or

1 equal to 150. And these LDL values are prior to
2 switching to protocol-mandated statin therapy. In
3 116, the LDL was greater than ATP III treatment
4 goals. In 117, the LDL was greater than or equal
5 to 100.
6 For trial 116, the statin intolerance was
7 defined as subjects who had tried at least two
8 statins and were unable to tolerate any dose or an
9 increase in statin dose above a total weekly
10 maximum dose specified in the protocol due to
11 intolerable muscle symptoms. Key exclusion
12 criteria are also listed for reference and will be
13 discussed in more detail in the safety section of
14 this talk.
15 Similar to the 12-week trials, the 52-week
16 trial also evaluated evolocumab in four different
17 patient populations whose background therapy was
18 based upon their screened LDL, their NCEP ATP III
19 risk category, and statin therapy at screening.
20 Background therapy consisted of four groups.
21 The first group was no drug therapy
22 required, and this was the diet-alone group. The

1 second group, low-dose drug therapy required. This
2 was atorvastatin 10 milligrams. Third group,
3 high-dose drug therapy required; this was
4 atorvastatin 80. And the last group was the
5 maximal drug therapy required, and that was the
6 atorvastatin 80 plus ezetimibe.
7 At the end of a four-week lipid
8 stabilization period, if participants still
9 exceeded the goal LDL value for their NCEP risk
10 category, they underwent background therapy,
11 up-titration to the next therapy level, and entered
12 an additional four-week stabilization period after
13 which study eligibility based on LDL was
14 reassessed.
15 Subjects were then randomized 2 to 1 to
16 evolocumab 420 milligrams once a month versus
17 placebo. The goal of this trial design was for
18 participants to be at ATP III goal before
19 evolocumab therapy was added. It's important to
20 note trial 109 allowed for patients who are at ATP
21 III goal by diet alone or by atorvastatin 10
22 milligrams alone to be randomized to evolocumab.

1 The four 12-week trials that evaluated the
2 efficacy of evolocumab were heterogeneous and
3 varied in terms of baseline CHD risk,
4 cardiovascular risk factors such as diabetes and
5 hypertension, and baseline LDL. Some notable
6 differences among the trials is that the
7 monotherapy trial 114 was primarily composed of
8 individuals at low or moderate CHD risk and had
9 only a small percentage of individuals with risk
10 factors such as diabetes and hypertension.
11 The statin-intolerant trial 116 and the HeFH
12 trial 117 had a greater percentage of individuals
13 with high CHD risk. Baseline LDL levels were
14 lowest in a statin combination trial 115 and
15 highest in the statin-intolerant trial, which is
16 116.
17 Baseline statin therapy varied among the
18 trials. No participants received statin therapy at
19 baseline in the monotherapy trial 114, and
20 participants were randomized to statin therapy at
21 baseline in the statin combination trial 115.
22 In trial 116, which evaluated evolocumab

1 compared to ezetimibe in patients with statin
2 intolerance, 82 percent were not receiving a statin
3 at baseline. In trial 117, which evaluated
4 evolocumab in participants with HeFH, approximately
5 75 percent of participants were taking high
6 intensity statins.
7 This slide looks at the demographics in the
8 52-week trial in the four different treatment
9 groups as well as in the overall trial. In the
10 52-week trial, participants were assigned to one of
11 four background therapies based on their NCEP risk
12 categories and screening LDL.
13 As participants were titrated to LDL goal
14 using one of the protocol specified regimens based
15 on their baseline CHD risk, there were expected
16 differences in baseline coronary heart disease
17 demographics and baseline LDL among the four
18 protocol determined background therapy groups.
19 As shown in the table, 64 percent of
20 participants assigned to atorvastatin 80 milligrams
21 plus ezetimibe 10 milligram therapy were at high
22 NCEP risk as opposed to only 5 percent in the

1 diet-alone group. Those receiving atorvastatin
2 80 plus ezetimibe were more likely to have coronary
3 artery disease, cerebrovascular disease and
4 diabetes.
5 However, in the overall evaluation of the
6 trial demographics, the majority of patients,
7 64 percent, were at moderate or low CHD risk, and
8 only 26 percent were considered at high risk for
9 coronary heart disease. Only 15 percent of
10 participants had a history of coronary heart
11 disease with less than 8 percent having a history
12 or prior myocardial infarction.
13 Only 4 percent of participants had a history
14 of cerebrovascular or peripheral arterial disease
15 with less than 1 percent having a history of prior
16 stroke. While almost half had a history of
17 hypertension, only 12 percent overall had a history
18 of diabetes.
19 This long-term trial enrolled many
20 participants at low or moderate CV risk. Thus, the
21 overall trial population does not represent a
22 population at high cardiovascular risk with

1 substantial cardiovascular disease burden.
2 The indication for individuals with HoFH is
3 supported by two trials, trial 233, which is
4 placebo controlled and had 49 participants, and the
5 ongoing open label extension trial 271 with 96
6 participants with HoFH. Trial 233 used an
7 evolocumab dose of 420 milligrams once a month
8 added onto other lipid-lowering therapies,
9 although lipid apheresis was not allowed.
10 The ongoing trial 271 used doses of
11 420 milligrams once a month and 420 milligrams
12 every 2 weeks, and apheresis was allowed. The
13 duration of exposure is 12 weeks in trial 233 and
14 84 weeks in trial 271.
15 For the HoFH participants, the mean age was
16 approximately 30 years, and almost half of the
17 participants were female. Approximately 45 percent
18 of the participants had a history of coronary
19 artery disease. Per protocol, all participants
20 were using a statin at baseline, and most were also
21 using ezetimibe.
22 The LDL values remained elevated with mean

1 values greater than 300 milligrams per deciliter in
2 the non-apheresis participants and approximately
3 280 milligrams in the apheresis participants.
4 Of the 99 HoFH participants in one or both
5 studies, 14 percent are adolescents between the
6 ages of 12 and less than 18 years of age, and 10
7 participated in both studies. Eleven were
8 non-apheresis subjects, and 3 were apheresis
9 subjects.
10 I'll now turn to efficacy. The LDL percent
11 change from baseline as compared to control is
12 shown on this slide and the next one for the four
13 12-week trials. In the monotherapy trial 114,
14 evolocumab use yielded an LDL reduction of 55 to
15 57 percent. For comparison, high intensity statins
16 such as atorvastatin 40 to 80 milligrams or
17 rosuvastatin 20 to 40 milligrams yield LDL
18 reductions ranging from 48 to 64 percent according
19 to their prescribing information, and some of these
20 doses have proven benefit in cardiovascular outcome
21 trials.
22 The results presented on this slide show

1 that evolocumab 140 milligrams every 2 weeks and
2 420 once a month dose yield similar LDL reductions.
3 The two different dosing regimens were designed by
4 the applicant to cater to the patient's preference
5 of taking the injectable every 2 weeks versus every
6 four weeks and not to allow titration of the
7 magnitude of the LDL reduction.
8 In the statin combination trial, shown on
9 this slide, evolocumab added onto different doses
10 and types of statins yielded LDL reductions
11 compared to placebo that ranged from 68 to
12 76 percent for the 140 every 2-week dosing and from
13 55 to 71 percent for the 420-milligram monthly
14 dosing.
15 In the 52-week trial 109, the percent change
16 in directly measured LDL from baseline to week 52
17 for evolocumab at the 420-milligram once a month
18 dose compared with placebo was negative 57 percent
19 when added to background therapy.
20 As shown in the table, compared with
21 placebo, the treatment difference for the percent
22 change from baseline at week 52 in LDL for the

1 evolocumab group varied somewhat among the
2 different background therapies. It was negative
3 56 percent in the diet-alone group, negative
4 62 percent in the atorvastatin 10 milligram group,
5 negative 57 percent in the atorvastatin
6 80-milligram group, and negative 49 percent in the
7 atorvastatin 80 plus ezetimibe group.
8 Statistically significant reductions in LDL
9 from baseline occurred during the first 12 weeks on
10 study from participants treated with evolocumab,
11 and these reductions were maintained through
12 week 52 for the four treatment groups.
13 This forest plot shows that evolocumab was
14 effective in reducing LDL across the phase 3 trials
15 relative to placebo and to ezetimibe.
16 I will comment on some of the secondary
17 endpoints that are summarized on this slide.
18 Across the trials, evolocumab in both dosing
19 regimens yielded statistically significant
20 reductions in non-HDL cholesterol at weeks 12 and
21 week 52. The estimated reduction from evolocumab
22 ranged from 50 percent to 62 percent greater across

1 the studies in two dosing frequencies.
2 For apolipoprotein B compared with placebo,
3 the estimated reduction from evolocumab ranged from
4 44 to 57 percent greater across the studies and the
5 two dosing regimens. For triglycerides and VLDL,
6 the results were not statistically significant for
7 both dosing regimens in all studies.
8 I'm now going to discuss the efficacy
9 results in the HoFH population. The percent change
10 from baseline in LDL at week 12 was used as the
11 primary efficacy endpoint in trial 233 for the
12 indication of HoFH. Trial 233 was a phase 3
13 double-blind placebo-controlled trial in
14 49 participants, 33 on evolocumab and 16 on
15 placebo. Mean serum concentration of LDL at
16 baseline was 349 milligrams per deciliter.
17 Compared with placebo, evolocumab resulted
18 in statistically significant reductions in LDL of
19 approximately 31 percent at week 12. Compared to
20 baseline, the mean percent change in LDL was
21 negative 23 percent for evolocumab and 8 percent
22 for placebo.

1 The secondary and exploratory endpoints are
2 summarized on this slide. Compared with placebo,
3 evolocumab resulted in statistically significant
4 reductions in ApoB of approximately 23 percent at
5 week 12. The changes in lipoprotein(a) did not
6 reach statistical significance.
7 Trial 271 is an ongoing open label long-term
8 extension trial in participants with familial
9 hypercholesterolemia, including but not limited to
10 HoFH. Participants with HoFH who completed trial
11 233 and those with FH who rolled over from other
12 trials, or had not received treatment in any trial,
13 were eligible to participate in this extension
14 trial.
15 Participants on apheresis as well as those
16 not on apheresis were eligible for the trial. Mean
17 LDL at baseline was 321 milligrams per deciliter.
18 Evolocumab resulted in LDL reductions of
19 19 percent at week 12 and 23 percent at week 24 in
20 the HoFH analysis set. In the non-apheresis HoFH
21 population, 25 participants have received at least
22 12 weeks of evolocumab 420 milligrams once monthly,

1 and then switched to 12 or more weeks of evolocumab
2 420 milligrams every 2 weeks.
3 Increasing the frequency of dosing from
4 420 milligrams every month to 420 milligrams every
5 2 weeks in participants with HoFH was associated
6 with approximately 6 percent greater reduction of
7 LDL.
8 This slide shows the trend in LDL reduction
9 over time in three groups in the open label
10 extension study. The bottom black line represents
11 the non-apheresis subjects who remain on
12 420 milligrams once a month. The red dashed line
13 represents the apheresis subjects who remain on
14 420 milligrams every 2 weeks. The blue line
15 represents the 25 participants who were on
16 420 milligrams every month for at least 12 weeks
17 and then up titrated and received 12 weeks of
18 420 milligrams every 2 weeks.
19 The trend over time among patients who
20 titrated from the every 4-week to every 2-week
21 dosing suggests a slightly greater mean LDL change
22 at week 24 than week 12. However, there are

1 limitations to this comparison.
2 First, there is confounding by time effects.
3 Differences between changes at weeks 12 and 24 may
4 be due to the effect of titration or to the effect
5 of additional time on treatment. And second, since
6 only those patients with insufficient changes in
7 LDL at week 12 titrated to the every two-week
8 dosing frequency, regression to the mean might also
9 explain the greater decrease in LDL observed at
10 week 24.
11 Efficacy conclusions. Evolocumab provided
12 robust decreases in LDL and other lipid parameters
13 across the four 12-week trials. The evolocumab
14 420-milligram every 2-week dose and the
15 420-milligram every month dose yield similar LDL
16 reductions.
17 The persistence of efficacy of the
18 420-milligram monthly dose was demonstrated in the
19 52-week trial 109. Evolocumab was effective across
20 all subgroups with no significant differences.
21 In the placebo-controlled HoFH trial 233,
22 which did not allow lipid apheresis treatment,

1 evolocumab compared to placebo significantly
2 reduced LDL from baseline to week 12 by 31 percent.
3 The mean change from baseline to week 12 within the
4 evolocumab arm alone was negative 23 percent.
5 This degree of LDL reduction compared to
6 baseline is similar to what has been observed with
7 statins and mipomersen but less than that observed
8 with lomitapide and LDL apheresis.
9 In the open-label extension trial,
10 evolocumab resulted in LDL reductions of 19 percent
11 at week 12 and 23 percent at week 24 in the HoFH
12 population. Increasing the frequency of dosing
13 from 420 milligrams once a month to 420 milligrams
14 every 2 weeks in participants with HoFH was
15 associated with a slightly greater mean LDL change
16 at week 24 than week 12. However, there were
17 several limitations to this comparison.
18 I'm now going to move on to safety. I will
19 discuss the evolocumab exposure in the safety
20 database and some of its limitations. I will then
21 present an overview of the adverse events. I will
22 focus on several concerns that were explored during

1 the safety review.
2 The applicant has used three different time
3 periods to describe the data for the safety
4 analysis of evolocumab. The initial trial
5 comprises integrated data from the 11 short-term
6 phase 2 and phase 3 trials in addition to the
7 52-week trial 109. The year 1 standard of care
8 controlled open label extension period comprises
9 integrated data from the year 1 control period of
10 the open-label extension studies.
11 After participating in any of the phase 2 or
12 phase 3 trials, participants can enroll in the
13 open-label extension phase 2 trial 110 or the
14 open-label extension phase 3 trial 138,
15 respectively. Upon entering the year 1 open-label
16 extension study, participants were re-randomized
17 2 to 1 for their first year of the study to a
18 standard of care plus evolocumab versus standard of
19 care control arm.
20 In trial 110, participants received either
21 evolocumab 420 milligrams once a month plus
22 standard of care or standard of care alone in

1 year 1, and then switched to evolocumab
2 420 milligrams once a month starting in year 2.
3 In trial 138, participants received either
4 evolocumab 140 every 2 weeks or the 420 once a
5 month dose plus standard of care versus standard of
6 care alone in year 1, and then switched to
7 evolocumab 140 every 2 weeks or 420 once a month
8 starting in year 2.
9 Beginning in the second year, after
10 completing the year 1 open label extension trial,
11 participants can enter the year 2 open label
12 extension period where all subjects are assigned to
13 evolocumab.
14 For the primary hyperlipidemia group, at the
15 time of database cutoff for the BLA submission,
16 which is April of 2014, approximately 3300
17 participants had been on the to-be-marketed doses
18 of evolocumab for at least 6 months, 1800 for at
19 least 12 months, and 600 for 2 years or more.
20 Participants with the following conditions
21 have been treated with the to-be-marketed doses of
22 evolocumab for at least one year: 350 participants

1 with established cardiovascular disease; 500
2 participants at NCEP ATP III high risk for
3 cardiovascular disease; 150 participants at
4 moderately high risk for cardiovascular disease;
5 180 with diabetes; 460 on concomitant high
6 intensity statin; and 560 on concomitant moderate
7 intensive statin. And there were 440 participants
8 that were 65 years or older.
9 The exposure to study drug is presented in
10 this table. The mean duration of evolocumab
11 exposure in the 140 every 2 week and the 420 once a
12 month treatment groups was 2.6 months and
13 5.3 months, respectively. The greater duration of
14 exposure in the once monthly dose was due to
15 trial 109, which was 52 weeks in duration, and
16 participants were administered only the 420 once a
17 month dose.
18 The median duration of evolocumab exposure
19 in the 140 every 2 week and the 420 once a month
20 treatment groups was 2.8 months.
21 The population included in the initial
22 trials had a mean age of 58 years, and 30 percent

1 were 65 years or older. Approximately 50 percent
2 were female, and 83 percent were white.
3 Approximately 19 percent had a prior diagnosis of
4 coronary artery disease, 2 percent stroke,
5 51 percent hypertension, and 13 percent had a
6 history of type 2 diabetes.
7 Approximately 34 percent of subjects were at
8 high and 10 percent were at moderately high CHD
9 risk by ATP III, and 30 percent were at moderate
10 risk.
11 Approximately 30 percent of the population
12 studied was on high intensity statin, and 38
13 percent were on moderate intensive concomitant
14 statin therapy. The baseline LDL ranged from 119
15 to 194 milligrams per deciliter with an average of
16 127 milligrams per deciliter.
17 The median duration of exposure to control
18 or evolocumab for the year 1 standard of care
19 control period was 7.4 months instead of 12 months
20 because the studies were still ongoing at the time
21 of the BLA submission.
22 Some of the limitations of this open-label

1 extension studies included reporting bias by either
2 patients or investigators and that the open-label
3 extension studies represent a select and smaller
4 group of patients who tolerated therapy in the
5 randomized trial and agreed to participate in the
6 open-label extension study.
7 With respect to exclusion criteria, some
8 important populations were excluded such as those
9 individuals with recent major cardiovascular
10 events, significant congestive heart failure,
11 significant hepatic or renal disease, type 1
12 diabetes, and newly diagnosed or poorly controlled
13 type 2 diabetes.
14 The HoFH population was exposed to
15 evolocumab at doses of 420 milligrams either every
16 2 weeks or once a month in trials 233 and 271. In
17 trial 271 involving a total of 96 participants with
18 HoFH, there were 69 HoFH participants who received
19 evolocumab for at least 3 months and 47 who
20 received evolocumab for at least 6 months. The
21 median exposure to evolocumab was 5 months.
22 Trial 233 included 11 participants with HoFH

1 who were between the ages of 12 and 17, and trial
2 271 included 10 of those 11 adolescents, plus an
3 additional 3 participants. All 14 subjects were
4 diagnosed with HoFH.
5 Exposure to the 420-milligram every 2-week
6 dose. Two groups of participants in study 271
7 received evolocumab 420 milligrams every 2 weeks.
8 First was the non-apheresis participants who began
9 the study on 420 milligrams once a month and
10 subsequently had their dose up-titrated to
11 420 milligrams every 2 weeks as allowed by
12 protocol, and two were the apheresis participants,
13 all of whom began on the 420-milligram every 2-week
14 dose.
15 Overall, there were 61 participants with
16 HoFH who have received the evolocumab 420-milligram
17 every two-week dose.
18 As of the 120-day safety update, there were
19 28 participants with HoFH who have been exposed to
20 the 420-milligram every 2-week dose for a median of
21 7 months, and 47 participants have been exposed to
22 the 420 monthly and 2-week dosing for a median of

1 12 months.

2 This table presents a summary of the adverse
3 event findings in the four 12-week phase 3 trials
4 and the one 52-week trial. Within each trial,
5 there were no marked disparities between treatment
6 groups and deaths, serious adverse events, or
7 adverse events leading to discontinuation.

8 Of note, the statin-intolerant trial had the
9 highest percentage of adverse events and adverse
10 events that led to discontinuation of
11 investigational product regardless of the treatment
12 group.

13 There were 15 deaths reported during the
14 clinical program of which 11 were deemed to be
15 cardiovascular in nature. As shown on the slide,
16 the incidence of deaths and cardiovascular deaths
17 was balanced between the two treatment groups in
18 the initial trials and the year 1 open-label
19 extension study.

20 In the integrated initial trials, serious
21 adverse events were reported by 2.4 percent of
22 participants in the placebo group, 2.1 percent in

1 the control group, which includes both the placebo
2 and the ezetimibe control groups, and 3 percent of
3 participants in the evolocumab every 2-week and
4 once-a-month dosing group.
5 Although the numbers are small, there was a
6 numeric increase in the evolocumab group in the
7 incidence of cardiac disorders, particularly angina
8 and myocardial infarction, pancreatitis,
9 appendicitis, pneumonia, and back pain.
10 In the year 1 standard of care control
11 period, 5.8 percent of participants in the standard
12 of care alone group and 5.4 in the evolocumab plus
13 standard of care group reported a serious adverse
14 event. The most common serious adverse events were
15 arthritis, angina pectoris, and myocardial
16 infarction, which occurred in less than 0.5 percent
17 in both groups.
18 In the HoFH trial 271, there were 7 or 7.3
19 participants who reported a serious adverse event,
20 and most of these events were cardiac in nature.
21 In the integrated initial trials, the incidence of
22 adverse events leading to permanent study drug

1 discontinuation was slightly higher in the
2 evolocumab group at 2.2 percent as compared to the
3 placebo group at 1.6 percent, but similar to the
4 any control group at 2.3 percent.
5 There were small increases in the adverse
6 event preferred terms of nausea, which was seen in
7 the evolocumab group compared to the control
8 groups.
9 In the year 1 standard of care control
10 period, 2 percent of participants in the evolocumab
11 group reported an adverse event leading to
12 discontinuation. The standard of care group did
13 not receive a control study drug, so there were no
14 discontinuations due to study drug in this group.
15 The most common event was myalgia with 7
16 participants or 0.2 percent.
17 In the year 2-plus, uncontrolled open label
18 extension period, 1 percent of subjects reported an
19 adverse event leading to discontinuation of
20 evolocumab. Adverse event preferred terms that may
21 be drug related included angioedema, drug eruption,
22 and pruritus.

1 In the integrated initial trials, which
2 combines the phase 2 trials and phase 3 trials, the
3 incidence of adverse events in the placebo and
4 evolocumab groups were similar at approximately
5 50 percent.
6 As shown in the table, the most common
7 adverse events where the incidence in the
8 evolocumab group was greater than the placebo in
9 any control groups were upper respiratory tract
10 infection, back pain, influenza, and nausea.
11 For the year 1 standard of care control
12 period, the incidence of adverse events was greater
13 in the evolocumab group. The most common adverse
14 events where the incidence in evolocumab group was
15 greater than the standard of care group included
16 nasopharyngitis, upper respiratory tract infection,
17 arthralgia, back pain, hypertension, and influenza.
18 I'm now going to move on to some adverse
19 events of special interest for this review, and the
20 first topic will be diabetes.
21 There's been some recent interest and
22 supportive data in the literature suggesting that

1 the LDL receptor may play a role in the risk of
2 developing type 2 diabetes. In addition, PCSK9 and
3 LDL receptors are expressed in insulin producing
4 pancreatic islet beta cells, and there's been some
5 animal data suggesting that this may have an effect
6 on the function of these cells.
7 To evaluate for a potential increase in
8 diabetic events on study drug, an analysis was
9 performed using reported adverse events consistent
10 with new onset diabetes. A search strategy using a
11 standard MedDRA query or SMQ for hyperglycemia and
12 new onset diabetes was used to identify potential
13 cases.
14 The incidence of potential diabetes events
15 was low in the initial trials, 0.8 percent in the
16 both the placebo and the evolocumab group. It was
17 slightly increased in the year 1 standard of care
18 control period with evolocumab plus standard of
19 care being 2.1 percent versus standard of care
20 alone, 1.6 percent.
21 To further explore the potential for
22 diabetes, the incidence of new onset diabetes and

1 diabetes-related adverse events was evaluated among
2 all patients, patients with baseline impaired
3 fasting glucose, and patients with baseline normal
4 glycemia.
5 Subjects were excluded from this analysis if
6 there was evidence of diabetes at baseline. In
7 addition, subjects who developed new onset diabetes
8 in one of the initial trials were excluded from the
9 year 1 standard of care controlled analysis.
10 New onset diabetes was defined using
11 laboratory, adverse event, and concomitant
12 medication data for the initial trials and in the
13 year 1 standard of care controlled period. Of
14 note, there were small differences in baseline
15 characteristics of evolocumab and control groups in
16 both study periods with a slightly higher incidence
17 of baseline hemoglobin A1c greater than or equal to
18 6.5 percent in subjects randomized to evolocumab.
19 As shown in the table, the incidence of new
20 onset diabetes was slightly increased in the
21 overall group, which was primarily due to the
22 impaired fasting glucose group. In the baseline

1 impaired fasting glucose group, the incidence of
2 post-baseline new onset diabetes was 2.6 percent in
3 placebo versus 3.1 percent in the evolocumab group.
4 In the year 1 standard of care controlled
5 studies in the overall and the impaired fasting
6 glucose group, there was an increase in the
7 incidence of new onset diabetes. In the baseline
8 impaired fasting glucose group, the incidence in
9 post-baseline new onset diabetes was 2.4 percent in
10 the control group versus 3.3 percent in the
11 evolocumab group.
12 In summary, in the longer duration trials in
13 patients with impaired fasting glucose at baseline,
14 there was a slightly greater proportion of
15 evolocumab treated patients who met criteria for
16 new onset diabetes by adverse event, laboratory
17 data, or initiation of medications for the
18 treatment of diabetes. For the majority of
19 patients, their glycemic status remained stable.
20 Changes in glucose homeostasis are monitorable and
21 treatable.
22 With statins, we believe that the modest

1 diabetogenic effect is outweighed by the
2 cardiovascular event reduction, which has been
3 shown in cardiovascular outcomes statin trials in
4 patients with diabetes.
5 The next adverse event of special interest
6 is pancreatitis. There is no convincing animal
7 data of drug-related gallbladder or pancreas
8 pathology. As of July of 2014, there were 7
9 participants with 8 events of pancreatitis, and all
10 were exposed to evolocumab at some point prior to
11 the pancreatitis event.
12 There were three cases of pancreatitis in
13 the initial trial, 0.8 percent for evolocumab
14 versus 0 percent in control. The remaining five
15 events occurred during the open label extension
16 period. Three occurred in the evolocumab group,
17 and two occurred in the control group. These two
18 cases in the control arm did have an exposure to
19 evolocumab in the initial trials, but evolocumab
20 exposure was unlikely to be a factor in these
21 cases.
22 In conclusion, the incidence of pancreatitis

1 in the clinical development program was low
2 overall, but all cases had current or remote
3 evolocumab exposure. While one cannot rule out
4 evolocumab as a contributing factor in these cases,
5 a review of the individual cases shows that they
6 were confounded by other risk factors such as
7 concurrent alcohol use, diabetes, gallstones,
8 recent endoscopic procedures, and concomitant
9 medications associated with pancreatitis.
10 Neurocognitive findings. One of the
11 theoretical safety issues is related to cognitive
12 function in patients who achieve very low levels of
13 circulating LDL cholesterol with PCSK9 therapy.
14 The blood-brain barrier does limit access of large
15 molecular sized products such as the monoclonal
16 antibody evolocumab to the central nervous system.
17 In addition, brain cholesterol is derived by
18 de novo synthesis as the blood-brain barrier
19 prevents access to cholesterol carrying
20 lipoproteins from the circulation. This should
21 allow the brain to remain largely independent from
22 circulating levels of cholesterol.

1 However, because there have been reports of
2 cognitive impairment associated with the use of
3 statins, the potential for neurocognitive events
4 was also explored with the PCSK9 inhibitors. To
5 examine this potential cognitive safety issue more
6 thoroughly, a search was done of neurocognitive-
7 related adverse event terms that included deliria
8 including confusion, cognitive and attention
9 disorders and disturbances, dementia and amnestic
10 conditions, disturbances in thinking and
11 perception, and mental impairment disorders.
12 For the initial trials, 11 participants
13 reported neurocognitive adverse events.
14 0.3 percent were in the any control group, and
15 0.1 percent were in the any evolocumab group.
16 For the year 1 standard of care controlled
17 open-label extension period, there were 19
18 participants who reported neurocognitive adverse
19 events. Three, or 0.2 percent, of participants
20 were in the control group, and 16 or 0.6 were in
21 the evolocumab group.
22 Thirteen of the 16 participants in the

1 evolocumab group had at least one risk factor
2 associated with neurocognitive events such as
3 previous memory loss, history of depression,
4 concurrent statins, benzodiazepine use, gabapentin
5 use, and topiramate use. For the majority of the
6 cases, treatment with evolocumab was continued
7 without interruption.
8 To explore whether drug-induced LDL could be
9 associated with increased neurocognitive events,
10 analysis of adverse events were performed by
11 achieved LDL subgroup. It is important to note
12 that these are not randomized comparisons. As very
13 few participants on placebo or ezetimibe achieved
14 low LDL, it is difficult to make meaningful
15 comparisons between the control and the evolocumab
16 groups. However, since randomized comparisons are
17 not possible in this analysis, it does allow for a
18 comparison of adverse events in the evolocumab low
19 LDL group versus evolocumab higher LDL group.
20 Baseline characteristics in the LDL
21 subgroups were overall similar to those in the
22 general study population. However, some

1 differences were noted for the LDL less than
2 40-milligram per deciliter group as compared to the
3 LDL greater than or equal to 40-milligram per
4 deciliter group, and included, one, that their
5 baseline LDLs were lower; two, there was more
6 baseline statin use and more use of moderate and
7 high intensity statins; and lastly, there was a
8 slightly greater percentage of subjects with
9 coronary artery disease, diabetes, or hypertension.
10 For the initial trial period and the year 1
11 standard of care controlled period, there were few
12 nervous system or psychiatric disorder adverse
13 events, and there was no notable imbalance among
14 the LDL subgroups.
15 A review of the patient narratives for the
16 LDL less than 40 milligram per deciliter and
17 neurocognitive events such as amnesia and memory
18 impairment show that many of these cases were
19 confounded by other conditions or medications that
20 could also affect cognitive function. Many of
21 these participants also had an LDL greater than
22 40 milligrams per deciliter just prior to the

1 event.

2 Thus, it is difficult to definitely

3 attribute the neurocognitive adverse event to

4 evolocumab versus another drug or preexisting

5 condition. In addition, these evaluations lack any

6 prospective neurocognitive testing.

7 Now, I'm going to move on to safety in the

8 low LDL subgroup. As mentioned previously, the

9 population who achieved LDL values less than

10 40 milligrams per deciliter tended to be at higher

11 CHD risk and received more intense background

12 statin therapy. Of note, this is an exploratory

13 analysis and is not a comparison of randomized

14 groups.

15 The safety information and adverse data from

16 this period reflects a median exposure of only

17 about three months of controlled data. For the

18 initial trials, there were no remarkable findings

19 in the different subgroups regarding common adverse

20 events and serious adverse events. There does not

21 appear to be a signal for nervous system or

22 psychiatric disorders or diabetic adverse events by

1 achieved LDL subgroup.

2 This slide describes the reported adverse
3 events in the evolocumab LDL subgroups during the
4 year 1 controlled open-label extension period. The
5 safety information and adverse event data from this
6 period reflects a median exposure of 7.4 months of
7 controlled but open-label data. The results should
8 be interpreted with caution, as one evolocumab
9 treated subgroup may not be representative of the
10 other.

11 In the one-year open-label extension trials,
12 the nervous system adverse events were low and
13 balanced between the LDL subgroups. There was a
14 small increase in adverse events of diabetes in the
15 lower LDL subgroup.

16 Anti-evolocumab antibody formation. From
17 the phase 2 and phase 3 studies supporting the
18 indication in patients with primary hyperlipidemia,
19 including the open label extension studies, there
20 was a low incidence of participants who developed
21 binding antibodies after at least one dose of
22 evolocumab, 0.1 percent, which was 7 out of 4,846

1 patients.
2 Four out of these 7 subjects were
3 transiently positive, meaning they were negative at
4 the last time point tested for a subject, and none
5 of the subjects developed neutralizing antibodies.
6 From the two studies supporting the
7 indication in patients with HoFH, none of the
8 subjects developed anti-evolocumab antibodies.
9 There were no serious adverse events that were
10 temporally associated with a positive binding
11 antibody result. There does not appear to be a
12 temporal correlation between the development of
13 binding antibodies and specific adverse events such
14 as hypersensitivity.
15 Now, moving to hypersensitivity. Using the
16 hypersensitivity MedDRA SMQ search strategy, which
17 has adverse event terms possibly associated with
18 hypersensitivity such as dermatitis, rash,
19 urticaria, and angioedema, the incidence of
20 potential hypersensitivity events was low overall,
21 but slightly higher in the evolocumab group
22 compared to the control groups.

1 In the initial trials, the incidence of
2 hypersensitivity was 2.4 percent in the placebo and
3 any control group, and evolocumab was 3.2 percent.
4 In the year 1 standard of care control period,
5 control was 3.3 percent, and evolocumab was
6 4.4 percent. And in the year 2 uncontrolled
7 open-label extension period, it was 5.7 percent.
8 There were 9 events of drug hypersensitivity
9 reported by 8 participants, 6 of which were in the
10 evolocumab-treated group. Four of these cases were
11 believed to be related to antibody administration
12 and one was to prednisone administration. One case
13 was related to evolocumab administration.
14 This case involved a 68-year-old male in the
15 statin-intolerant trial. He had a history of hay
16 fever, hiatal hernia, hypertension, and
17 esophagitis. Sixteen days after the first dose and
18 one day after the last dose of evolocumab prior to
19 the event, he reported swelling of the throat and
20 sore throat. He received two additional doses of
21 evolocumab over the next four weeks.
22 These two adverse events led to the

1 withdrawal of evolocumab. Both events were
2 reported as resolved the day following the last
3 dose of evolocumab.
4 Musculoskeletal issues. In the initial
5 trials, adverse events for the musculoskeletal and
6 connective tissue disorder system organ class were
7 reported in 12.8 percent in the placebo group and
8 14.6 percent in the evolocumab group. The most
9 common adverse events where there was an increase
10 in the evolocumab group as compared to placebo were
11 back pain and myalgia.
12 In the year 1 standard of care controlled
13 open-label extension period, 15 percent of
14 participants in the control group and 19 percent in
15 the evolocumab group reported a musculoskeletal
16 adverse event. The most common adverse events
17 where there was an increase in the evolocumab group
18 were arthralgia, back pain, myalgia, and pain in
19 extremities.
20 In addition to adverse events, we also
21 examined laboratory data, particularly creatine
22 kinase elevations. In the initial trials, CK

1 elevations greater than 5 times and 10 times the
2 upper limit of normal were balanced among the
3 placebo, the any control, and the evolocumab
4 groups.
5 In the year 1 standard of care controlled
6 open-label extension period, the incidence of CK
7 elevations greater than 5 times and 10 times the
8 upper limit of normal was greater in the control
9 group as compared to the evolocumab group.
10 Most of these participants who had
11 significant post-baseline elevations in CK had
12 confounding factors such as the development of
13 severe hypothyroidism, muscle and joint injuries,
14 tendinitis, and concomitant statin therapy that may
15 have contributed to the events.
16 However, in the phase 1 studies, which
17 enrolled healthy individuals not on concomitant
18 statin therapy, there were two reports of CK
19 greater than 10 times the upper limit of normal,
20 which may have been drug related.
21 This slide summarizes a case from a phase 1
22 study 121. In the first case, a white male

1 developed an elevated CK 22 days after the single
2 dose of 210 milligrams of evolocumab, and the CK
3 was 51 times the upper limit of normal on day 24.
4 On day 26, the CK was near normal and returned to
5 baseline 21 days after the start of the adverse
6 event. The creatine remained normal throughout.
7 He had an associated activity of walking at
8 a car show. I agree with the investigator's
9 assessment that evolocumab exposure was likely a
10 contributing factor.
11 In the second case, in a phase 1 PK
12 equivalence study with prefilled syringes and auto
13 injectors, a non-serious case of rhabdomyolysis was
14 reported in a 26-year-old black male. This
15 participant had elevated CK levels at screening and
16 at baseline. He received 2 doses of evolocumab
17 140 milligrams separated by approximately 8 weeks.
18 On the day of the second and final dose of
19 evolocumab, his CK was elevated at 1.6 times the
20 upper limit of normal, but this was less than his
21 baseline value of 2.1 times the upper limit of
22 normal.

1 At the end of study visit which was 56 days
2 after the second dose, the adverse event of
3 rhabdomyolysis was reported at which time his CK
4 level was greater than 15 times the upper limit of
5 normal. His CK levels peaked at 62 times the upper
6 limit of normal about three days later.
7 Approximately 2 weeks after the peak CK, the
8 adverse event was reported to be resolved, and the
9 CK levels had decreased to baseline values. The
10 rhabdomyolysis adverse event did not require
11 hospitalization and was not associated with muscle
12 symptoms. No other adverse events were reported
13 for this participant.
14 These two cases in healthy individuals not
15 on concomitant statin therapy suggests that
16 evolocumab may contribute to CK increases when used
17 as monotherapy.
18 Hepatic issues. In the initial trials in
19 the year 1 standard of care control period, serious
20 adverse events and adverse events for the
21 hepatobiliary disorder system organ class were
22 balanced between the control and the evolocumab

1 groups.

2 As shown on this slide, the incidence of
3 transaminase elevations was low and similar in the
4 initial and extension trials for both the control
5 and evolocumab group. In the initial trials, there
6 was no participant who had both an ALT or an AST
7 greater than 3 times the upper limit of normal and
8 a total bilirubin greater than 2 times the upper
9 limit of normal at any study visit.

10 In the year 1 standard of care controlled
11 open-label extension period, 2 participants in the
12 evolocumab group had transaminase levels that were
13 3 times the upper limit of normal and had either a
14 total bilirubin greater than 2 times the upper
15 limit of normal or an IRI greater than 1.5.

16 In the first case, the abnormalities
17 occurred three days after the participant admitted
18 himself to rehabilitation for alcohol
19 detoxification and was not believed to be related
20 to evolocumab.

21 In the second case, the participant was
22 receiving evolocumab 420 milligrams once a month as

1 well as simvastatin, nitrofurantoin, ramipril,
2 along with other medications. She developed an ALT
3 of 24 times the upper limit of normal with a normal
4 bilirubin approximately 2 months after starting
5 evolocumab. Evolocumab and simvastatin were
6 stopped.
7 Approximately 6 weeks later and one week
8 after endoscopy gastroscopy procedure, she had a
9 total bilirubin of 9 times the upper limit of
10 normal and an ALT and AST about 20 times the upper
11 limit of normal. A liver biopsy was performed and
12 was consistent with drug-induced acute hepatitis.
13 Approximately 2 months later, the LFT
14 abnormalities resolved. Nitrofurantoin was
15 suspected as a possible cause of the LFT
16 abnormalities per the investigator as well as
17 evolocumab, simvastatin, diclofenac, and ramipril.
18 Cardiovascular events. This slide shows the
19 number of participants with any positively
20 adjudicated cardiovascular event as well as some of
21 the individual events that comprise the total from
22 the 52-week trial. I believe that this trial

1 provides the most robust long-term safety
2 assessment since it was double blind and placebo
3 controlled.
4 The incidence of participants with
5 positively adjudicated cardiovascular events was
6 low overall, reflecting a population in which many
7 patients were not at high cardiovascular risk, as
8 well as the fact that they were treated to LDL
9 goal, if possible, prior to adding evolocumab.
10 During the treatment period, there were only
11 2 deaths, one from cardiac failure and the other
12 from myocardial infarction. Both were in the
13 evolocumab group. A third death adjudicated as
14 sudden cardiac death occurred 21 days after the end
15 of the study, which was 49 days after the last dose
16 of evolocumab. Only one non-fatal myocardial
17 infarction was reported, and this was in a patient
18 being treated with evolocumab.
19 In conclusion, the number of positively
20 adjudicated cardiovascular events from the
21 long-term placebo-controlled trial is too small to
22 make any reliable conclusions regarding

1 cardiovascular risk reduction. Although I am not
2 showing the data here, a review of the adjudicated
3 cardiovascular events from the open-label extension
4 period did not suggest an increase in
5 cardiovascular risk.
6 The safety of the 420-milligram every 2-week
7 dose. This slide summarizes the adverse event data
8 with the 420-milligram every 2-week dose in the
9 HoFH population. Although the number of
10 participants in the groups are small, in the 120
11 safety update, which has a data cutoff of July of
12 2014, the incidence of adverse events was greater
13 in the subgroup of 28 HoFH participants who only
14 received 420 milligrams every 2 week dosing
15 compared with the incidence in the other two
16 subgroups by dosing regimen. This was also true
17 for the serious adverse events.
18 There were more adverse events in the
19 420-milligram every 2-week group related to
20 injection site reactions such as erythema, pain,
21 hematoma, and bruising, than were reported in the
22 every month dose group.

1 There are limitations to this analysis as
2 the every 2-week only group was the group receiving
3 apheresis, and this group had a higher
4 cardiovascular risk at baseline compared to the
5 non-apheresis group. The apheresis group due to
6 the apheresis schedule also had more frequent
7 protocol specified visits than those participants
8 who started out with once a month dosing.
9 This trial was not designed to provide
10 informative data regarding the efficacy and safety
11 profile between the two different dosing regimens
12 in the HoFH population.
13 This slide summarizes some of the efficacy
14 benefits that were discussed at the beginning of
15 the talk. Evolocumab 420 milligrams once a month
16 results in statistically significant reductions in
17 LDL of approximately 60 percent after 12 and
18 52 weeks of treatment. Evolocumab at doses of 140
19 every 2 weeks and 420 every month yields similar
20 LDL reductions.
21 In patients with HoFH, evolocumab
22 420 milligrams once a month compared to placebo

1 significantly reduced LDL from baseline to week 12
2 by 31 percent. The mean LDL reduction from
3 baseline to week 12 within the evolocumab arm alone
4 was 23 percent. Increasing the dosing frequency
5 from 420 milligrams once a month to every 2 weeks
6 is associated with a small additional LDL
7 reduction.
8 The effect of evolocumab on cardiovascular
9 morbidity and mortality in any population has not
10 been determined.
11 In the safety summary, there were no marked
12 disparities between treatment groups in deaths,
13 serious adverse events, or adverse events leading
14 to discontinuation. The safety database for the
15 140-milligram every 2-week dose and the
16 420-milligram once a month dose is limited in
17 long-term placebo-controlled data.
18 The 52-week placebo-controlled trial
19 enrolled many participants at low or moderate CV
20 risk. Thus, the overall trial population does not
21 represent a population at high CV risk with
22 substantial cardiovascular disease burden on

1 maximally tolerated statin therapy, arguably the
2 most appropriate patient population for add-on
3 therapy to a statin.
4 The limited amount of safety and efficacy
5 data is problematic for the 420 milligram every
6 2-week dose, especially as this dosing regimen
7 could potentially be used in children aged 12 years
8 or older.
9 There were no major safety signals
10 identified in this review. However, evolocumab has
11 the potential for widespread use. Therefore, even
12 small differences in serious safety signals, if
13 true, could have significant public health
14 implications.
15 Potential safety signals, based on the data
16 we have today, include a small increased incidence
17 in pancreatitis and hypersensitivity skin-related
18 adverse reactions; a possible increase in new onset
19 diabetes in those with baseline impaired fasting
20 glucose; musculoskeletal events and CK elevations,
21 which may have been confounded by concomitant
22 statin use; transaminase elevations and

1 hepatobiliary adverse events, which may have been
2 confounded by concomitant use of statins and other
3 medications; and adverse reactions that may be
4 related to chronic low levels of LDL induced by a
5 drug that have yet to be identified.
6 Finally, I would like to acknowledge my
7 colleagues who provided considerable support for
8 this review. Thank you.
9 **Clarifying Questions**
10 DR. SMITH: Thank you, Dr. Craig.
11 We now have time for some questions, and
12 again, specifically, these should be clarifying
13 questions, and we'll initially target them to the
14 FDA. We may have some time for the sponsor later.
15 So Dr. Nason.
16 DR. NASON: Thanks. I just wanted to
17 understand, there are some differences in the
18 numbers between the sponsor's presentation and the
19 FDA presentation. And specifically, I'm looking at
20 the FDA slide 107 that focuses on low LDL. I'm
21 looking at those below 40 and those above 40
22 compared to the sponsor's slide. Oh, sorry. I'm

1 doing it backwards, the sponsor's 107 versus the
2 FDA's 60.
3 I am just trying to understand both the
4 total number of people are a little bit different,
5 and then the percentages for, say, diabetes, the
6 sponsor was looking at 2.3 versus 3.5, I guess, in
7 the low versus not so low LDL groups. And in the
8 FDA, we're talking much lower percents, although
9 maybe a similar difference of .6 versus 1.5.
10 So I just wanted to understand whether one
11 was more recent date or it was a different subset
12 of the people.
13 DR. CRAIG: The sponsor can clarify, but I
14 think they're slightly different analyses. The one
15 that I have here, the data cutoff is at the time of
16 the BLA submission. They may have used a
17 later -- their cutoff may have been later with the
18 120 safety update, and they may have done a
19 slightly different analysis.
20 I'm just looking at preferred terms from
21 different MedDRA SOCs, and I think they used high
22 level group terms, which is similar to the analysis

1 that I presented under the neurocognitive. So some
2 of it -- I could ask the company to confirm, but I
3 think it's the data cut, and that the analysis is
4 slightly different. But I think the signal is sort
5 of the same. It's very small. It might be a
6 signal. It's small.
7 DR. WASSERMAN: I would agree. Slide up.
8 So the data that was shown on CS 107, in terms of
9 the new onset diabetes, it's from the 120-day
10 safety update. Again, we felt it was very
11 important, from the sponsor's point of being
12 transparent, to show you our most current data.
13 And so we wanted to make sure that that was shown.
14 So for new onset diabetes, that has a four-
15 component definition. It includes having two
16 fasting blood glucoses of greater than 126, a
17 hemoglobin A1c of greater than 6.5. You can also
18 have diabetes adverse events or initiating a new
19 anti-diabetic medication.
20 So our definitions are a little bit
21 different, but I think we would agree with
22 Dr. Craig that while there's no definitive signal,

1 I don't think we can rule one out, which is why
2 we're going to continue to look at that going
3 forward in our ongoing studies as well as in our
4 ongoing cardiovascular outcomes study.
5 DR. SMITH: Dr. Burman.
6 DR. BURMAN: Just two points of
7 clarification, please. On page 31 of your nice
8 presentation, did you do any statistical analysis
9 on the post-baseline new onset diabetic differences
10 in the two groups? Page 23. I'm sorry.
11 DR. CRAIG: I think I did comment that there
12 was -- in the evolocumab group at baseline, there
13 were a slightly higher percentage of patients on
14 evolocumab that had a higher hemoglobin A1c than
15 the control group.
16 So there is -- oh, between the 2.6 and 3.1?
17 No, we didn't do a statistical analysis between
18 those two numbers.
19 DR. BURMAN: And then a second point of
20 clarification, if I might. On slide 77, on
21 page 39, the adverse events in the safety analysis
22 of 420 milligrams every 2 weeks, 82 percent versus

1 61 percent, could you comment on the type of those
2 adverse events?
3 DR. CRAIG: I don't have a listing of the
4 adverse events right here. I think that serious
5 adverse events were more cardiac in nature. My
6 review of -- I'd have to go back to my briefing
7 document. There wasn't, I think, any big disparity
8 between them.
9 To be honest, I'm not sure if this is real
10 or not or if it's just a small sample size. So I
11 don't think there was anything in the adverse
12 events that really struck me, as there was a big
13 difference between the dosing regimens.
14 DR. SMITH: Dr. Hiatt.
15 DR. HIATT: This is a follow-up question to
16 Dr. Nason. I think the point's been made. It had
17 to do with the diabetes risk. And in looking at
18 the sponsor's background document, and as you
19 presented in your slides, you show the risk of
20 diabetes between evolocumab and the comparator, as
21 just absolute rates. But the risk ratios are
22 helpful.

1 FDA, you presented it mostly as just the
2 numbers, which numerically don't look like there's
3 much going on. But if you look at the FDA
4 background document, table 80, page 255 -- which I
5 wouldn't bring up, don't worry about that. But the
6 risk ratio approach, I think is helpful.
7 So if you look at the integrated patient
8 analysis set excluding study 109, going from
9 impaired fasting glucose to diabetes has a risk
10 ratio of 1.83, an upper bound of 3.83. Now, with
11 study 109, that same transition has a risk ratio of
12 0.70 for about a 1.39.
13 I think we've all conceded that the risk of
14 diabetes needs further study, and we discussed, I
15 guess, yesterday that knowledge of diabetes risk
16 with statins took some time. And it really wasn't
17 until the review of the JUPITER trial that we
18 understood that there was an association of statins
19 to diabetes. And I think it sounds like the
20 sponsor is committed to also explore that.
21 So I guess my only additional point on this
22 is when we look at adverse events, they're

1 experiential. They're descriptive. And when you
2 just look at columns and columns of numbers, it's
3 sometimes hard to see subtle differences.
4 I would encourage you to use the risk ratio
5 in addition to the absolute numbers and the
6 confidence intervals because the upper bound of the
7 confidence interval reflects two things. It
8 reflects the certainty of how much risk can be
9 excluded with that amount of data at this moment in
10 time, and it also reflects the number of events.
11 So the fewer the events, the greater the
12 boundary is, of course. But it gives us a sense of
13 how much certainty and uncertainty we're left with
14 safety data to date.
15 So the more risk ratio presentations from
16 both the sponsor and the FDA, I think it makes it
17 clear for the advisory committee to make a better
18 assessment of how much further we need to go, if
19 you will, to better understand signals that we
20 think might be there but haven't really been
21 demonstrated to any degree of clarity in the
22 current database.

1 DR. SMITH: So what I'd like to do now is
2 open up for questions, clarifying questions that
3 may be directed to the sponsor as well as to the
4 FDA. And, Dr. Cooke, you earlier had a question?
5 DR. COOKE: Yes, I have two lines of
6 questions, and maybe I'll start with kind of
7 following up this diabetes risk question
8 What data do you have regarding changes in
9 insulin sensitivity, either insulin levels, HOMA
10 levels or whatever, on therapy?
11 DR. WASSERMAN: Sure. I'd like to ask
12 Dr. Rob Scott to come up to the microphone.
13 DR. SCOTT: thank you. And perhaps I can
14 make a few introductory comments. Dr. Hiatt has
15 appropriately pointed out that we're not in a
16 position to exclude a signal at the moment, and we
17 agree that this is a question that will need to be
18 answered. We are adjudicating new onset diabetes
19 in the outcomes study. So with probably around
20 1500 events, we'll be in a better position to talk
21 about that.
22 The question about diabetes really arises,

1 too, because statins have been shown to increase
2 the incidence of diabetes. And the FDA pointed out
3 that there is a school of thought that thinks
4 up-regulation of the LDL receptor in the pancreas
5 is a potential explanation.
6 I would say that the predominant theory is
7 that changes in protein prenylation as a
8 consequence of modifying the cholesterol synthesis
9 pathway. And that impact on protein such as the
10 glucose transport protein is likely to blame.
11 In statin studies, we see an increase in
12 body weight, which could cause insulin resistance,
13 and this has been borne out in studies looking at
14 HMG coA reductase, SNPs. So it's pretty clear that
15 statins increase the amount of insulin and caused
16 an increase in insulin resistance.
17 Slide up, please. Here are data showing the
18 HOMA-IR in different patient populations, patients
19 with diabetes, impaired fasting glucose, metabolic
20 syndrome, and patients without any disturbance of
21 glucose tolerance. And you can see that there's
22 clearly no signal there that suggests that there's

1 an increase in insulin resistance.
2 The next slide -- slide up, please -- looks
3 at the HOMA-B and shows you that at least using
4 this measure, that we're not able to see any impact
5 on HOMA-B as well. And if I showed you the raw
6 insulin data, you would get the same picture.
7 So clearly, there's no overall impact.
8 Whether there are some individual subjects that
9 have a different response, we're not able to answer
10 at this stage.
11 DR. COOKE: Thank you. The other line of
12 questions that I'd like to explore would be related
13 to the pediatric subjects in the homozygous FH
14 patients.
15 So it's clearly a small number of patients,
16 so I think we're going to have limited information.
17 But within those subjects, the 12 to 18, what can
18 you tell us about the pubertal stage of those
19 individuals?
20 DR. WASSERMAN: Dr. Stein, do you want to
21 make a comment on what we've seen in 271?
22 DR. STEIN: Thank you. Evan Stein from

1 Cincinnati. I think an important question is the
2 pediatric population. Firstly, in homozygous FH,
3 this is actually the largest number of pediatric
4 homozygous FH, including in any homozygous FH
5 trial.
6 For example, against the mipomersen and
7 lomitapide trial, there were no children under age
8 18 or no people under age 18 in lomitapide, and
9 there were 7 in the mipomersen trial.
10 We didn't do Tanner staging. The studies
11 are too short to see any change in Tanner age, but
12 they were 12 and above. We're following them long
13 term, but again, it would be fairly small. And as
14 you know, Tanner changes in children especially,
15 many of them were 15, 14, 16, already fairly
16 Tanner 3 or Tanner 4 stage.
17 DR. COOKE: Right. I agree there wouldn't
18 be an opportunity to observe for changes in Tanner
19 staging, but just knowing whether these were
20 children that were potentially early pubertal, mid
21 pubertal, late pubertal, that's an age range that
22 could easily span all of those.

1 DR. WASSERMAN: So let me try to deal with
2 your question, Dr. Cooke. So we realized in
3 retrospect that we did not obtain that data. We're
4 now going back within that study 271 and obtaining
5 that data retrospectively, and we will be
6 collecting it prospectively.
7 In addition, we are in the process -- as
8 Dr. Scott alluded to during the pharmacovigilance,
9 we have two randomized controlled studies that
10 we've done in FH pediatrics, and that will be an
11 instrumental part of those studies going forward.
12 So we understand your point. It's something
13 that we're going to do prospectively.
14 DR. COOKE: Okay. Great. Then just within
15 again that population, given the sort of one size
16 fits all dosing, recognizing a very limited
17 data set, is there anything that you can say about
18 the response to therapy? Did they have lower LDL
19 levels? I assume that none of these patients had
20 very low LDL levels, but was there anything
21 observed different compared to the adult subjects?
22 DR. WASSERMAN: So what I would say is

1 that -- slide up -- in terms of just the response,
2 these are the 14 adolescent homozygotes subjects.
3 You can see the response is a little bit less than
4 what we saw in the overall all homozygotes.
5 But that being said, some of these patients
6 were on apheresis. And as you're probably aware,
7 at that age if they're on apheresis, they have very
8 intractable disease. So they can be quite
9 challenging to treat.
10 So I think it's something that we'll follow
11 going forward, and obviously, as we acquire more
12 data, it will inform us better in this area
13 DR. SMITH: Dr. Blaha.
14 DR. BLAHA: Thank you.
15 I want to follow-up on CRP-related questions
16 that Dr. Burman asked earlier. I think, if I'm not
17 mistaken, when we saw that data earlier, we saw the
18 baseline CRP, but we didn't see the change in CRP.
19 If we could come back to that.
20 But in follow-up on that, of course, some
21 have speculated that on-treatment CRP levels,
22 including their lowering, such in the JUPITER

1 trial, they correlate with outcomes. And in the
2 IMPROVE-IT study, there was a mild reduction in
3 CRP. And people have been trying to study direct
4 inhibition of the inflammatory pathways as a
5 possible mechanism.
6 So I think this is at least somewhat
7 pertinent to the question of LDL as a surrogate.
8 So could you, after showing the CRP change data,
9 comment on the mechanism or the reason why there is
10 not an association between PCSK9 and CRP?
11 DR. WASSERMAN: So slide up. So I'll show
12 you what we've seen from our integrated parent
13 analysis in terms of changes from the initial study
14 baseline in CRP, and this is in milligrams per
15 deciliter. And you can see that looking at any
16 placebo versus any control, there really is no
17 appreciable signal.
18 I think part of it, it's a very good risk
19 factor in terms of a surrogate. In terms of
20 looking at a response, a clinically meaningful
21 response, it's a little bit challenging.
22 But I'd like to ask Dr. Scott to come up and

1 talk a little bit about his experience with CRP.
2 DR. SCOTT: Thank you. So as you know, it's
3 very important to look at specific CRP levels when
4 you're evaluating response. So people with a CRP
5 that's less than 1 generally don't respond to
6 statins either because their CRP levels are not
7 raised. And people with CRP levels greater than
8 10, one can usually assume that that rate of CRP is
9 due to some sort of intercurrent inflammatory
10 illness.
11 So you've really got to study people between
12 the 1 and the 3 range, and we really don't have
13 that many patients that -- having said that, we
14 don't see any signal for reductions in CRP.
15 The reasons as to why statins lower CRP are
16 still a little obscure. Some people feel that this
17 is a response to reduced inflammation in the
18 periphery, whereas other people feel that the
19 production of CRP in the liver is affected directly
20 by the cholesterol content inside hepatocytes
21 that's lowered by statins.
22 So it's not exactly clear how statins lower

1 CRP. We know they lower risk and they lower CRP,
2 and we know that high CRP is associated with high r
3 risk. All of the analyses that have looked at
4 whether CRP reductions are associated with
5 reductions in risk are totally confounded by the
6 fact that those reductions occur in people who are
7 responding to statins with a lower LDL.
8 So I would say the science is a little fuzzy
9 here, and we all know example of drugs that have
10 improved outcomes without lowering CRP.
11 DR. WASSERMAN: I'd also like to just add
12 again the point that I tried to emphasize with
13 Dr. Burman, which is we have an ongoing outcomes
14 study in which there will be a significant
15 percentage of people that have elevated CRP at
16 baseline. And I think that's going to be a
17 wonderful data set to be able to really address
18 your question in a rigorous fashion just like it
19 was done with IMPROVE-IT and ezetimibe.
20 DR. SMITH: Dr. Orza.
21 DR. ORZA: I had half a dozen questions for
22 the sponsor, and I have another half dozen for FDA.

1 But I'm going to try to combine and prioritize.
2 The first one for FDA is about the secondary
3 efficacy endpoints in your slides 20 and 22. And
4 I'm wondering -- I'm assuming that the studies were
5 adequately powered for these endpoints and that
6 also they were adequately controlled for multiple
7 tests. You can say if that's not true.
8 But I'm kind of wondering how we should view
9 the relationship between the LDL lowering endpoint
10 and these other endpoints? How important is it to
11 see, for example, a corresponding increase in HDL,
12 or how important is it to also see what's going on
13 with VLDL or the ApoB or ApoA1? How do we sort of
14 sort these all out to figure out
15 whether -- focusing just on the LDL --
16 DR. CRAIG: I would say that the LDL is
17 obviously the most important. Non-HDL, ApoB, total
18 cholesterol is not up there separately, often track
19 together with the LDL.
20 You can argue about -- I think some of these
21 other trials that have come out recently, you could
22 very well argue about the value of changes in

1 triglyceride and HDL and whether we think that
2 changes cardiovascular outcomes. So I think they
3 are not as important as -- it's really the LDL.
4 That's the main focus of this drug. It's an LDL
5 drug. I don't know if that helps you.
6 I mean, these are all the ones that the
7 company is asking for in their indication, or
8 either that or listed as their secondary efficacy
9 endpoints, but certainly, LDL is the most
10 important. Some of these other endpoints,
11 typically, if you see a robust decrease in LDL,
12 you're going to see a similar change with non-HDL,
13 ApoB, total cholesterol.
14 We are not as supportive of triglyceride and
15 HLD given some of the recent clinical trial data.
16 DR. ORZA: So is there enough here to
17 support also having those as part of the
18 indication?
19 DR. CRAIG: I don't think we're asking you
20 to weigh in on that today.
21 DR. ORZA: My second question was about
22 standard of care as a control and how well defined

1 that was and how much it could change over time for
2 any one patient.
3 DR. CRAIG: I actually would ask the
4 sponsor. Most of these patients were on
5 statin -- both groups were on statin therapy. The
6 standard of care was on statins. I don't have the
7 specific data on the percentage in the open-label
8 extension study.
9 DR. ORZA: Standard of care as a control,
10 there's a spectrum from very loosely defined to
11 very tightly defined, and I'm just wondering where
12 this fell in that spectrum.
13 DR. CRAIG: Well, I think that's part of the
14 problem with the open-label extension study. It's
15 not as nice and clean as a double-blind placebo-
16 controlled study.
17 I'm going to ask the sponsor if they have
18 specific information on how tightly the standard of
19 care control was.
20 DR. WASSERMAN: So slide up. Just to be
21 clear, this was a global program, and so every
22 country has its own, quote, unquote, "standard of

1 care." And every country and a lot of different
2 societies have their own guidelines as well. So
3 obviously, we wanted to be cognizant of that.
4 Taking into account the population that we
5 enrolled of which there are a thousand monotherapy
6 patients, and the reason that we did that was
7 because we felt it was really important to
8 understand how our drug behaved in the absence of
9 statins and in the absence of potential confounding
10 from statin intolerance. And so that is a very
11 rich data set to address some of the questions that
12 Dr. Craig had pointed out.
13 But I think you can appreciate that nearly
14 three-quarters are on statins and 20 percent are on
15 high intensity and 31 percent are on moderate
16 intensity, and then 13 percent are on ezetimibe.
17 So about 45 percent are high or moderately high by
18 NCP risk, and about 70 percent fit into the current
19 ACC-AHA guidelines in terms of statin benefit
20 groups.
21 If I can just show the next slide please.
22 There's a lot of concern around what happens when

1 patients go into these open label studies around
2 are doctors going to back titrate. And we share
3 the FDA's concern about physicians actually
4 behaving that way.
5 So we actually did the experiment to see
6 what would happen. This is data from study 138, so
7 this is our phase 3 open-label control. And you
8 can see the patients that are on a statin at any
9 time, and you can see that 90 percent that are on
10 evolocumab -- and remember that in this trial after
11 12 weeks, they can see the lipid levels. The
12 12 weeks of not seeing the lipid levels is to keep
13 the parent study blinded, the initial study
14 blinded. But after 12 weeks, they can change the
15 lipid-lowering therapy.
16 So what we saw is that 90 percent of the
17 patients stayed on their stable statin dose. You
18 saw about a 6 percent decrease in statin intensity,
19 a 3 percent increase, and then you can see what
20 happened in standard of care alone.
21 This amount of kind of changing and
22 modulation of statin intensity is very consistent

1 if you were to go to a Medicare database or a
2 commercial payer database. It has very, very
3 similar data in terms of statin up-titration and
4 down-titration.
5 DR. J. SMITH: Can we ask for a -- because
6 we haven't seen this before.
7 DR. WASSERMAN: Sure.
8 DR. J. SMITH: Do you have the data for your
9 phase 2 controlled study? Because -- or what's the
10 median duration for this?
11 DR. WASSERMAN: I will get that for you.
12 It's a valid question
13 DR. J. SMITH: Because we just raised that
14 because, as you mentioned, physicians didn't even
15 have access to lipid levels until three months into
16 this, and so only at that point could they even
17 contemplate whether or not they would make a
18 decision.
19 DR. WASSERMAN: We do have it. I know that
20 we do have it for the 110, the phase 2. I think in
21 that study, we did encourage people not to change
22 the background therapy.

1 Slide up. This is actually the commercial
2 database patient population. So on the left is an
3 overall 5 percent Medicare cut. Then you can see
4 MarketScan which is basically commercial payers.
5 You can see the 5 percent Medicare cut that we have
6 here is about 40,000 patients. The MarketScan data
7 is nearly 300,000 patients. And then on the right
8 are the patients within that that are actually on
9 lipid-lowering therapy. And if you look at the
10 bottom row, it's statin titration up and down and
11 no change.
12 So just looking at statins, regardless of
13 whether or not you're on evolocumab, which is
14 obviously not approved yet -- which is in the no
15 change. You see it's about 93 -- 94 percent don't
16 change, about 3 to 4 percent down-titrate, and
17 about 2 to 3 percent -- actually, in general,
18 3 percent up-titrate.
19 So at least from what we've seen to date,
20 it's very consistent with people's behaviors in the
21 absence of an approved PCSK9 inhibitor.
22 DR. SMITH: Just for clarity then, is that

1 satisfactory from FDA, or are there some data that
2 you would like to see this afternoon?
3 DR. CRAIG: Do you have a slide with the
4 data from the phase 2 that describes it?
5 DR. WASSERMAN: I'll see if I can get it for
6 you.
7 DR. SMITH: We'll revisit that after the
8 break or this afternoon.
9 DR. ORZA: My next question is for the
10 sponsor. The graphic that you showed in slide 114,
11 I felt was very nice, very clear. And I was
12 wondering if you had a similar display for the HoFH
13 population.
14 DR. WASSERMAN: It's a wonderful question.
15 It's one that we debated, and the problem was that
16 if we did it, the axis would go up to the roof. So
17 the difference that you see for statin-tolerant
18 patients is about 100 milligrams per deciliter.
19 That's what you'd see in HoFH, except that you'd be
20 starting at 350. So you'd be going from about 350
21 milligrams per deciliter down to 250 milligrams per
22 deciliter.

1 DR. ORZA: So that's how it looked if you
2 look at slide number 80.
3 DR. WASSERMAN: Yes, so slide up, which is
4 slide number 80. That's about a 94-milligram per
5 deciliter change, so that gives you a sense of the
6 magnitude of that change in that patient
7 population.
8 DR. ORZA: So they get down to about -- they
9 get down from about 350 to about 250?
10 DR. WASSERMAN: About 250, yes.
11 DR. ORZA: They're still at 250?
12 DR. WASSERMAN: Yes.
13 DR. ORZA: So that's my question, about is
14 that -- in terms of where they ultimately get to,
15 is that -- is the imperative just to be able to
16 reduce the LDL by any amount regardless of how
17 close you're getting them to the desired level?
18 DR. WASSERMAN: So these patients have a
19 genetic mutation in which both -- they have two
20 mutations that led to very, very high LDL levels.
21 In general, getting patients that have homozygous
22 FH down to levels of 250 is unheard of, and so this

1 is a really, really serious disease.
2 Prior to the advent of the statins, many of
3 these people died in childhood, in their teens.
4 And that's why when you saw the SAEs, you saw there
5 was a lot of atherosclerotic vascular disease. You
6 saw calcification of the aorta, calcification of
7 the aortic valve. It's a very serious illness.
8 DR. SMITH: Dr. Wilson had a question or
9 comment related to that.
10 DR. WILSON: Thank you very much. To
11 follow-up on Dr. Orza's question, that previous
12 slide that just went away, I would guess that
13 that's biphasic, that there are responders and
14 non-responders, so.
15 DR. WASSERMAN: So with homozygous FH, if
16 you are completely null for the LDL receptor, you
17 will not respond. And so that is true. There
18 is -- I wouldn't call it biphasic. There's
19 gradations. However, with PCSK9 inhibitors, if
20 you're able to fully inhibit PCSK9 and keep it
21 suppressed, you will achieve kind of a steady state
22 in terms of the number, in this case, in

1 homozygous FH, of the dysfunctional LDL receptors
2 that are capable of functioning.
3 So for that individual patient, there LDL
4 can be a little bit more stable, but in general,
5 homozygous FH in patients, their LDLs tend to be a
6 lot less stable than a non-homozygous FH patient.
7 DR. WILSON: I guess the question related to
8 that is how long does it take to figure out
9 somebody's a responder or a good responder? That's
10 where I was going.
11 DR. WASSERMAN: So you can tell within
12 basically -- within about four days after treating
13 the patient, they will have -- within four hours,
14 they get complete PCSK9 suppression. The rationale
15 behind the 420-milligram every 2-week dose is that
16 the patients that have homozygous FH have about
17 twofold higher PCSK9 levels than a non-homozygous
18 patient.
19 There's actually a gradation between non-FH
20 patients heterozygotes and then homozygotes. And
21 because the drug is supposed to bind PCSK9, if
22 there's a lot more PCSK9 around, you need a lot

1 more drug to be able to try to bind up that PCSK9
2 and get those LDL receptors up regulated.
3 DR. WILSON: So the other question I had in
4 general was metabolic safety information, which you
5 have, related to vitamin levels, whether you've
6 been vitamin supplementing.
7 Then at very low LDL cholesterol, especially
8 at those levels, you get acanthocytosis of red
9 cells, and hemoglobin A1c may no longer be as
10 valid. That point needs to be made as we go
11 forward for glycemic safety. So glucose data is
12 more valid perhaps at very low LDL cholesterol
13 levels than hemoglobin A1c.
14 Then finally, I've not seen any data related
15 to anemia or hematocrit at very low LDL
16 cholesterols. Is there any concern?
17 DR. WASSERMAN: So let me take the easy one
18 first with anemia. The only anemias we saw in this
19 clinical program were from GI bleeds, so that was
20 not an issue. And then I'll let Dr. Rob Scott come
21 up to the mic, and he'll walk you through our data
22 around vitamins.

1 DR. SCOTT: I hear the concern around
2 vitamins. And fat-soluble vitamins, I think the
3 concern arises from the fact that we all know that
4 fat-soluble vitamins are carried on ApoB containing
5 lipoproteins. In addition, we know that there are
6 defects in vitamin E metabolism in patients with
7 hypobeta or A beta lipoproteinemia.
8 So first of all, I'll just try and explain
9 to you why I think it's misplaced, and then I'll
10 show you some data that we have.
11 So firstly, vitamin E and other fat-soluble
12 vitamins gets trafficked out of the gut after
13 absorption on chylomicrons and VLDL. And it gets
14 re-exported out of the liver on VLDL. So the first
15 point is that, as you've seen, we have a rather
16 modest effect on VLDL and it's somewhat variable.
17 Then VLDL, once it's on VLDL, it rapidly
18 equilibrates with all of the other lipoproteins.
19 The kinetics of vitamin E transport to
20 tissues is more related to the concentration within
21 those lipoproteins rather than the absolute levels.
22 So if you give a drug that lowers LDL profoundly,

1 you will lower the amount of vitamin E that's in
2 LDL. But since it's only a proportion, we don't
3 see changes in other lipoproteins.
4 So first of all, slide up. So if you
5 normalize vitamin E for cholesterol levels, which
6 is the way we normally look at it, you can see that
7 there's no change in concentration of vitamin E
8 across the different -- across the LDL and HDL. In
9 fact, there's an increase in vitamin E
10 concentration in HDL.
11 So the first thing that we can say is that
12 vitamin E absorption and transport into HDL is
13 normal, but if you look at the bars there that say
14 RCM, those are red cell membranes. And this is a
15 valid way of looking at tissue stores or tissue
16 levels of vitamin E, and you can see that red cell
17 membrane, vitamin E doesn't change either.
18 So it doesn't seem to be an adverse impact
19 on vitamin E. So that goes towards answering the
20 question about acanthocytosis.
21 The two problems that you might think about
22 with the red cells is that if you lower vitamin E,

1 it might cause acanthocytosis, and clearly, we're
2 not impacting vitamin E levels in red cell
3 membranes.
4 Then with some other drug classes, such as
5 synthetic ApoA1 drugs that lower cholesterol and
6 can strip cholesterol out of red cells, you might
7 see crenellated red cells. We haven't seen any of
8 that in our program. We have not seen
9 acanthocytosis. Thank you.
10 I could actually also show you, just to put
11 this question to bed, the HDL levels of vitamin E
12 by achieved LDL just so you can see the most
13 extreme signal.
14 Slide up. Here is vitamin E levels in HDL
15 by LDLs from less than 15 to greater than 40. So
16 even at very low levels of LDL, we have not seen
17 any reduction in the ability to get vitamin E into
18 other lipoproteins or red cells, for instance.
19 DR. SMITH: We're now going to break for
20 lunch. We will have time this afternoon for
21 panelist questions that we haven't yet reached.
22 We'll reconvene again in this room at 1:00 p.m.

1 sharp.

2 Please take any personal belongings you may

3 want with you at this time. And, committee

4 members, please remember there should be no

5 discussion of the meeting during the lunch among

6 yourselves, with the press, or any member of the

7 audience. Thank you.

8 (Whereupon, at 12:04 p.m., a lunch recess

9 was taken.)

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1 A F T E R N O O N S E S S I O N

2 (1:00 p.m.)

3 **Open Public Hearing**

4 DR. SMITH: Good afternoon. I'd like to

5 welcome everyone back. We're going to open up with

6 the open public hearing component of this session.

7 Both the Food and Drug Administration, the

8 FDA, and the public believe in a transparent

9 process for information-gathering and

10 decision-making. To ensure such transparency at

11 the open public hearing session of the advisory

12 committee meeting, FDA believes that it's important

13 to understand the context of an individual's

14 presentation.

15 For this reason, FDA encourages you, the

16 open public hearing speaker, at the beginning of

17 your written or oral statement to advise the

18 committee of any financial relationship that you

19 may have with the sponsor, its product and, if

20 known, its direct competitors. For example, this

21 financial information may include the sponsor's

22 payment of your travel, lodging, or other expenses

1 in connection with your attendance at the meeting.
2 Likewise, FDA encourages you at the
3 beginning of your statement to advise the committee
4 if you do not have any such financial
5 relationships. If you choose not to address this
6 issue of financial relationships at the beginning
7 of your statement, it will not preclude you from
8 speaking.
9 The FDA and this committee place great
10 importance in the open public hearing process. The
11 insights and comments provided can help the agency
12 and this committee in their consideration of the
13 issues before them.
14 That said, in many instances and for many
15 topics, there will be a variety of opinions. One
16 of our goals today is for this open public hearing
17 to be conducted in a fair and open way where every
18 participant is listened to carefully and treated
19 with dignity, courtesy, and respect. Therefore,
20 please speak only when recognized by the
21 chairperson. Thank you for your cooperation.
22 So will speaker number 1 please step up to

1 the podium and introduce yourself? Please state
2 your name and any organization you are representing
3 for the record.
4 MR. CLYMER: Dr. Smith and members of the
5 committee, thank you for the opportunity to address
6 you today. I am John Clymer, executive director of
7 the National Forum for Heart Disease and Stroke
8 Prevention, a non-profit coalition of organizations
9 dedicated to preventing heart attacks and strokes
10 and reducing disparities.
11 Amgen, the FDA, and several other HHS
12 agencies are among the 85 members of the National
13 Forum who are drawn from the public, private, and
14 non-profit sectors. I have not personally received
15 any financial benefit from the sponsors.
16 In the days after the 9/11 and the anthrax
17 attacks, a wise public health leader helped policy
18 makers who were concerned about bioterrorism keep a
19 balanced perspective. She told them, "We face
20 urgent threats and urgent realities."
21 Well, today, you have an opportunity to
22 address an urgent reality. As the Department of

1 Health and Human Services Million Hearts Initiative
2 has highlighted, only one-third of people with high
3 cholesterol have it controlled. This contributes
4 to the 200,000 heart attacks suffered by Americans
5 that the CDC estimates are preventable.
6 One reason for the huge gap between the
7 Million Hearts goal, of 65 percent of the
8 population with high cholesterol having it
9 controlled and the 33 percent who do, is that for
10 some people, the array of medical and non-medical
11 therapies available today are insufficient or
12 cannot be tolerated.
13 Thus, the National Forum applauds the
14 development of new therapies that provide more
15 options to reduced people's risk for heart disease
16 and stroke. The National Forum is encouraged by
17 the efficacy data from the recent PCSK9 inhibitor
18 trials. We are optimistic that the risk of heart
19 disease in the U.S. can be reduced through safe and
20 effective new treatment options such as PCSK9
21 inhibitors in combination with behavioral,
22 educational, and other important initiatives and

1 efforts, and that these therapies will help bring
2 us closer to achieving the Million Hearts goal of
3 preventing heart attacks and strokes.
4 Two hundred thousand preventable heart
5 attacks and the human and economic burdens linked
6 to them is an urgent reality that calls for urgent
7 action.
8 DR. SMITH: Thank you.
9 Will speaker number 2 now please step up to
10 the podium? Please identify yourself and any
11 organization you may be representing.
12 MS. WILEMON: Good afternoon. My name is
13 Katherine Wilemon. I'm the president of the FH
14 Foundation, a non-profit research, advocacy
15 organization dedicated to increasing awareness of
16 FH. I also have FH, and I came to this work after
17 I had a heart attack in my late 30s, and then
18 discovered that my oldest daughter had also
19 inherited FH.
20 Thank you for this opportunity to speak to
21 you today on behalf of all of those living both
22 with heterozygous and homozygous FH. This

1 population is in dire need of additional therapies.
2 FH is one of the most common
3 life-threatening genetic conditions in the world.
4 Current estimates are that as many as 1 in 250
5 people have FH. FH can also be found in every race
6 and ethnicity.
7 FH is a diverse condition. There are more
8 than 1200 known mutations with varying impact on
9 LDL levels, but what defines FH phenotypically is
10 elevated LDL cholesterol and aggressive premature
11 heart disease.
12 Heterozygous LDL levels typically range, as
13 you know, from 200 to 400, and for homozygous FH as
14 high as 1,000. It is important to remember,
15 though, that individuals with FH have had these
16 significantly elevated atherogenic LDL levels from
17 birth. It is this cumulative burden that results
18 in extremely aggressive and often shockingly early
19 heart disease.
20 People who have heterozygous FH often suffer
21 heart attacks and invasive surgeries in their 20s,
22 30s, and 40s, and every male with FH has a

1 50 percent chance of having a heart attack by the
2 age of 50. Individuals with homozygous FH can
3 suffer from advanced coronary artery disease as
4 early as childhood with tragic outcomes.
5 Since the Nobel prize winning discovery by
6 Goldstein and Brown of the LDL receptor over
7 35 years ago, the FH population has afforded
8 scientists the opportunity to look at the
9 relationship of LDL to heart disease.
10 FH patients have been crucial in
11 conclusively proving that LDL cholesterol is causal
12 for atherosclerosis. Those with the highest LDL
13 cholesterol suffer the most accelerated and
14 catastrophic heart disease. FH patients are at
15 such high risk that they are often given
16 combination therapy, the kitchen sink approach:
17 high-dose statins, ezetimibe, bile sequestrants,
18 rigid low fat diets, and sometimes apheresis. And
19 yet, it cannot be stressed enough that we rarely
20 reach healthy LDL levels.
21 FH is also a family disease that is easily
22 passed from generation to generation. Each first

1 degree loved one of an individual with FH has a
2 50 percent chance of also inheriting this
3 life-threatening condition.
4 What gives us hope is that longitudinal
5 studies in FH patients have shown that early and
6 aggressive LDL lowering reduces our rate of cardiac
7 events and lengthens our lives.
8 There are two major barriers to adequate
9 care to people living with and often dying from FH.
10 In the U.S., more than 90 percent of the people
11 living with FH are undiagnosed. And for the only
12 10 percent who are lucky enough to be accurately
13 diagnosed, we have limited options.
14 The FH Foundation is hopeful that this new
15 class of PCSK9 inhibitors will represent an era of
16 hope for those of us who are at the front lines
17 fighting heart disease. And we do need to remember
18 this is the most deadly condition in modern times.
19 We urge you to consider more groundbreaking
20 research so that innovative, safe and effective
21 therapies will continue to become available for
22 those of us whose lives depend upon it. Thank you.

1 DR. SMITH: Thank you.
2 Will speaker number 3 please step to the
3 microphone? Please identify yourself and any
4 organization you may be representing.
5 DR. ALMASHAT. My name is Sammy Almashat.
6 I'm a physician with Public Citizens Health
7 Research Group. I have no conflicts of interest.
8 In an editorial published concomitantly with
9 the alirocumab and evolocumab studies in the New
10 England Journal of Medicine, the two authors, who
11 are also members of the ACC-AHA guideline
12 committee, pointed out two main concerns with the
13 approval of the drugs at this time.
14 One is obviously, there is no precedent for
15 the level of LDL reduction seen with these two
16 drugs, whether with statins or other therapies.
17 And the other concern, which is more central, is in
18 their opinion, it would be premature to endorse
19 these drugs for widespread use before the ongoing
20 randomized trials that are adequately powered,
21 unlike the preapproval trials, for outcomes are
22 completed. And they base this concern on results

1 from several previous non-statin trials as add-on
2 therapy to statin medications.
3 They referred also to the ACC-AHA guidelines
4 also responding to the recent ineffective
5 non-statin trials that point to a strong preference
6 for the use of non-statins that had been determined
7 to be safe and effective in randomized controlled
8 trials.
9 The FDA had similar concerns, pointing out
10 that the unexpected and disappointing results from
11 the recent trials for three different non-statin
12 therapies as add-on statin medications should at
13 least give us pause as we consider the use of lipid
14 biomarkers in the assessment of benefit/risk.
15 I'll go to this slide first. So it's useful
16 to point out that the recent non-statin trials that
17 the FDA was referring to were all as add-on therapy
18 to existing statin medications. As most of you
19 know, previous trials of monotherapy of niacin
20 showed niacin, too, to be effective in reducing
21 cardiovascular risk in the 1970s and '80s.
22 However, these trials were done as add-on therapy

1 as is the current FOURIER trial of evolocumab.
2 Three of these trials did show a significant
3 reduction in LDL beyond that seen with statins.
4 None of the trials showed an additional reduction
5 in cardiovascular risk beyond that seen with
6 statins. One of the trials was terminated early
7 because there was an increase in cardiovascular
8 risk.
9 Again, this is unexpected. These were all
10 unexpected results, and so that makes it even more
11 important to await the results of the FOURIER trial
12 before making any conclusions about evolocumab.
13 This slide points out the difference in size
14 and duration between the OSLER 1 and 2 trials
15 published recently in the New England Journal of
16 Medicine and the ongoing FOURIER trial, which is
17 adequately powered for cardiovascular events, and
18 the recently published IMPROVE-IT, which gives us
19 an alternative now to these two drugs as add-on
20 therapy to statins. Ezetimibe is effective in
21 reducing cardiovascular risk further beyond that
22 seen with statin therapies.

1 The displacement of statin therapy -- so I
2 was discussing add-on therapy. This slide
3 addresses the potential for monotherapy in place of
4 statin medications. And the FDA confirmed to the
5 sponsor that it is unlikely to consider a
6 monotherapy indication or an indication explicitly
7 referencing statin intolerance without positive
8 outcomes data, the unintended consequence of which
9 would be in the FDA's opinion that statin
10 intolerance as a clinical entity would likely be
11 promoted and marketed to the detriment of effective
12 statin therapy.
13 The medical officer pointed out that the
14 sponsor did not adopt the FDA's more stringent
15 definition of statin intolerance in the one trial
16 evaluating statin-intolerant patients. An overly
17 lax definition of statin intolerance like that seen
18 with trial 116 would make statin displacement even
19 more likely.
20 Finally, the homozygous familial
21 hypercholesterolemia population is obviously
22 different. There is no need for a cardiovascular

1 outcomes trial in these patients. However, the
2 trial that was done in these patients did not
3 compare evolocumab with the best current therapy of
4 apheresis.
5 The potential benefit of evolocumab would be
6 in addition to the best current therapy of
7 apheresis, however, that trial was not done. And
8 in the trial that was done, evolocumab had a lower
9 absolute reduction in LDL as compared to historical
10 rates with apheresis.
11 In addition, almost all of the patients in
12 the homozygous trial were not LDLR negative/
13 negative. And given the mechanism of the drug, the
14 FDA concluded that it is likely that the treatment
15 of the entire homozygous population after approval
16 would be less than that seen in the clinical trial.
17 In conclusion, we think the approval of
18 evolocumab would add to the list of agents
19 currently on the market that reduce LDL but that
20 have no evidence for cardiovascular benefit for at
21 least two or three years. If we wait for the
22 FOURIER trial, we would ensure that this did not

1 happen, and we would also set a new precedent for
2 the approval of LDL-lowering agents on the basis of
3 actual cardiovascular benefit.
4 I ask the committee to imagine themselves
5 three years from now when the results of FOURIER
6 are released and what situation the medical
7 community would be in were this trial to show that
8 evolocumab is not effective on cardiovascular
9 outcomes.
10 This drug would have already been
11 established as standard medical care, and the
12 difficulty of weaning physicians and patients off
13 an ineffective therapy should that happen is great,
14 and that is why we ask the committee to wait for
15 the outcome of that trial.
16 DR. SMITH: Thank you.
17 Will speaker number 4 now please step up the
18 microphone? Please identify yourself and any
19 organization you may be representing.
20 MS. McCREADY: Hi. I'm Colleen McCready,
21 and I appreciate this opportunity to tell my story
22 to this panel in the hopes that it will have a

1 positive impact on the outcome. In the interest of
2 full disclosure, the FH Foundation paid my travel
3 expenses, but I volunteered my time to be here.
4 I was 14 when it was first discovered that
5 my lipid levels were not within a normal range. It
6 took 20 years before my condition was treated, and
7 I was diagnosed as HoFH. I started on the
8 strongest statin available, which cut my LDL in
9 half, which was not close to acceptable levels. I
10 had serious side effects, being unable to walk and
11 rhabdomyolysis.
12 I tried all the others in various doses, in
13 various combinations with other drugs. I had
14 muscle pain with a couple of them, with little to
15 no lowering of my lipids. I tried for three years
16 with no positive outcome.
17 I then started on an orphan drug while my
18 total cholesterol was over 400. It worked great.
19 I finally had a drug that worked that dropped me to
20 almost normal levels. My constant companion, my
21 fear of having a fatal heart attack, subsided
22 finally, until my liver enzymes came back five

1 times higher than normal, so I had to cut back on
2 my dosage.
3 Now, my levels are climbing back up. My
4 constant companion is back. I worry now again
5 every day. I have never had a heart attack, and I
6 would like to avoid it at all costs. I have had a
7 coronary calcium score done, and I have 70-plus
8 year-old arteries. I'm 38 years old.
9 I don't have a lot of options without these
10 new PCSK9 inhibitors. Do you know what it's like
11 to feel like that? I look into my children's eyes
12 every day and pray for another day with them. I
13 have a life and a career and a family and a list of
14 things I want to do. I want to live. I have so
15 many things I want to do before I die, but every
16 day death is such a part of my life.
17 These new drugs represent hope to myself and
18 many others. I, we, need that hope very much.
19 Thank you.
20 DR. SMITH: Thank you.
21 Will speaker number 5 now please step to the
22 microphone? Please identify yourself and any

1 organizations you may be representing.
2 MR. RADABAUGH: Hello. My name is Scott
3 Radabaugh. I'm a volunteer patient advocate for
4 the FH Foundation. I work as a human resources
5 manager for Pacific Gas and Electric in the San
6 Francisco Bay area, and I'm a father of three great
7 kids, Luke, Hannah and Chloe.
8 As for disclosure, the FH Foundation helped
9 me with some of my travel expenses today so that I
10 could attend, and I'm a patient in a clinical trial
11 for a PCSK9 inhibitor. However, I don't know if
12 I'm getting the placebo or the real drug. And I
13 have no financial relationship with any drug or
14 healthcare organization.
15 In the time it takes me to finish my five
16 minutes, five people in America will die from heart
17 disease. I dream of a world where heart disease is
18 a thing of the past and no one will experience the
19 grief of suddenly losing a loved one and also being
20 cheated out of the opportunity to say goodbye.
21 My high cholesterol was discovered at age 27
22 by having a routine physical. At the time, my high

1 cholesterol was 300. After taking my first statin,
2 my cholesterol dropped into the 200s. From what I
3 was doing, I was told that I had reduced my level
4 of risk of a heart attack to that of the general
5 population.
6 At the time, everyone thought that high
7 cholesterol was an adult lifestyle disorder. No
8 one realized cholesterol could be genetically
9 driven or that my cholesterol system had been
10 exposed to dangerously high levels of cholesterol
11 since the day I was born.
12 At age 43, I was three minutes into a cardio
13 workout on an elliptical machine when I start to
14 feel a burning sensation in the center of my chest.
15 I stopped my workout, called my doctor, went to the
16 hospital for a stress test, and soon after, I was
17 being prepped for a quadruple bypass.
18 After recovering from a six-hour surgery,
19 the surgeon told me, "You're very, very lucky. You
20 were just about two to three weeks away from having
21 a fatal heart attack." In the hospital recovering
22 from surgery, one of my nurses suggested that I

1 should have my kids checked, and I followed her
2 advice.
3 On April 11th, 2012, I started the day with
4 plans to celebrate my one-year anniversary of
5 surviving quadruple bypass. Instead, I was at UC
6 San Francisco hearing the words "familial
7 hypercholesterolemia" for the very first time.
8 I still remember the crushing feeling to
9 hear that I had unknowingly passed on FH to all
10 three of my kids, but the conversation soon became
11 much worse as the doctor told me that one of my
12 children had homozygous FH.
13 I was speechless as the doctor told me that
14 children as young as 3 can have heart attacks from
15 this stuff and that without aggressive treatment,
16 life expectancy is adolescence.
17 Later that day, I should have been out
18 celebrating my own year of bonus time. However, I
19 found myself at home thinking as a father, this is
20 the cruelest of all jokes, that my life was saved
21 only to watch my child die.
22 At age 4, my youngest child had a

1 cholesterol level of 800 and an LDL of 690. She
2 had so much cholesterol in her body that
3 cholesterol oozed out in the form of xanthomas on
4 her ankles, elbows, and hands. Some painful
5 xanthomas on her ankles had to be surgically
6 removed.
7 Since then, I've had a carotid
8 endarterectomy, and two years after my bypass, I've
9 learned that two of my four bypass graphs have
10 already failed. I've got additional blockage in my
11 heart, and my doctor, he wants me to get my LDL to
12 a level of 70 or less.
13 So if you look at my family picture over
14 there, our combined total cholesterol is 1800
15 before treatment. Today we're at 800. So
16 amazingly, 1,000 points of risk have been taken
17 away from my family. However, none of us are at
18 our target levels yet.
19 As I stand here today, I realize that I was
20 allowed to live not to just watch my child die but
21 to help save her life. As a parent, there is no
22 better feeling than this. However, I can't do it

1 alone. I'm asking for your help in providing more
2 treatment options for my kids and the countless
3 other children who need more tools to combat this
4 terrible genetic disorder. Thank you.
5 DR. SMITH: Thank you.
6 Will speaker number 6 please step to the
7 microphone? Please introduce and state any
8 organizations you may be representing.
9 MS. PACKARD-MILAM: Thank you. My name is
10 Michele Packard-Milam. I'm the executive director
11 of Mended Hearts and Mended Little Hearts. Mended
12 Hearts is a 501(c)(3) charitable non-profit
13 organization. We are the largest cardiovascular
14 peer-to-peer support network in the world. We do
15 receive sponsorships from most of the major
16 cardiovascular drug manufacturers, but no one paid
17 for me to be here. My time is being paid by Mended
18 Hearts as are my travel expenses.
19 FH runs in my family. My mother died at 48
20 from FH, and I think my son has it, and we're
21 having trouble getting him diagnosed. So this is
22 both a professional and personal issue for me.

1 We have 20,000 members operating out of 300
2 chapters across the United States and Canada. We
3 are in 460 hospitals where we visit about 215,000
4 patients every year.
5 We focus on education, peer support, and the
6 key to what we do is to empower patients to take
7 charge of their own health and to actively
8 participate in their medical decisions.
9 Understanding cholesterol is one of the most
10 important things that we try to help them do.
11 We've been doing this for 64 years.
12 This panel in addressing the new
13 FDA-regulated prescription drug to treat
14 cholesterol, particularly for patients who are
15 statin resistant or who have FH, needs to consider
16 a number of things. The speakers before me have
17 done an excellent job of talking about the
18 statistics, but it's just so important to remember
19 that heart disease is still the number one killer
20 in the United States, killing more people every
21 year than the top five cancers combined.
22 Heart disease is getting younger, meaning

1 that more U.S. citizens are being diagnosed with
2 high cholesterol at younger ages, including many of
3 our children. This relates to childhood obesity.
4 And high cholesterol, especially LDL-C cholesterol,
5 is one of the most persistent building blocks of
6 cardiovascular disease.
7 We think it's important for medical
8 professionals and healthcare providers to have as
9 many tools to manage cholesterol as they possibly
10 can, especially for young patients and those for
11 whom the current treatments are ineffective.
12 We know education is a very important part
13 of this, and we're trying to do our part to make
14 that better. But the more tools the doctors have,
15 the more likely we are to be able to manage
16 cholesterol in a way that prevents so many deaths
17 every year.
18 Mended Hearts is speaking today to support
19 innovation and treatments for heart disease and to
20 express our support for the companies that are
21 making the investment and developing these new
22 options for patients.

1 We further hope that in our process you will
2 consider issues of accessibility for patients on
3 fixed income and with limited access to advanced
4 medical care facilities. Our members and the
5 patients we serve deeply appreciate your hard work
6 in analyzing these new treatment options. We
7 really thank you.
8 DR. SMITH: Thank you.
9 Will speaker number 7 please step to the
10 microphone? Please state your name for the record
11 and any organization you may be representing.
12 DR. deGOMA: Good afternoon. Thank you for
13 the opportunity to speak at the open public hearing
14 today. My name is Emil deGoma. I'm a
15 cardiologist, lipidologist, and medical director of
16 preventive cardiology at the University of
17 Pennsylvania.
18 Our program under Dan Rader has a long
19 history of caring for patients with familial
20 hypercholesterolemia and other high-risk
21 dyslipidemias, including statin intolerance. I
22 actively treat about 200 FH patients in our clinic,

1 and many more are treated by my Penn colleagues.
2 Regarding disclosures, I conduct contracted
3 research at the University of Pennsylvania in
4 collaboration with the sponsors presenting data on
5 PCSK9 inhibitors. I have the privilege of working
6 together with the FH Foundation. My trip today,
7 though, is not being funded by the FH Foundation or
8 any sponsor.
9 I'm here to help represent FH patients and
10 patients with statin intolerance, as well as the
11 healthcare providers who take care of these
12 high-risk patients. My comments pertain equally to
13 both PCSK9 inhibitors discussed this week.
14 Reducing the burden of cardiovascular
15 disease associated with familiar
16 hypercholesterolemia requires better diagnosis and
17 better treatment. Better diagnosis is earlier
18 diagnosis. Identifying FH at a young age provides
19 the opportunity to minimize cumulative exposure to
20 high LDL and prevent atherosclerosis. We and
21 others are exploring strategies to attempt to close
22 the detection gap.

1 Better treatment involves additional
2 effective and well tolerated LDL-lowering therapies
3 above and beyond the existing armamentarium. The
4 treatment gap is substantial. In the U.S.,
5 preliminary data is available from the FH
6 Foundation's CAscade FH Registry, a nationwide
7 registry launched in 2013.
8 In a cross-sectional analysis of almost 1300
9 adult FH patients enrolled in 10 lipid centers
10 across the United States, only 25 percent of
11 patients had an LDL cholesterol less than
12 100 milligrams per deciliter at time of enrollment,
13 only 25 percent.
14 Despite combination therapy in almost half
15 of patients, a minority achieved an LDL cholesterol
16 reduction greater than 50 percent, and the mean
17 on-treatment LDL cholesterol was above
18 150 milligrams per deciliter.
19 In addition to FH, unmet need is substantial
20 among a different high-risk group,
21 statin-intolerant patients. While overall,
22 limiting side effects associated with statins are

1 rare, implications for outcomes are significant.
2 Optimal medical therapy in these individuals
3 is severely handicapped. Without statins, we lose
4 the opportunity to reduce major vascular events by
5 35 percent or more.
6 Statins were an essential component, if not
7 the acknowledged centerpiece, of medical therapy in
8 the landmark COURAGE trial that demonstrated the
9 effectiveness of medical therapy alone compared
10 with an initial invasive approach in patients with
11 stable coronary artery disease.
12 PCSK9 inhibitors are effective LDL-lowering
13 therapies. Studies of human genetics support the
14 mechanism as athero protective, and in exploratory
15 analyses of each of the two PCSK9 inhibitors, a
16 50 percent reduction in cardiovascular events was
17 observed. These data provide some insight into the
18 effects of PCSK9 inhibition on cardiovascular
19 outcomes, which are being formally tested in
20 ongoing randomized trials.
21 Both PCSK9 inhibitors would be welcome
22 additions to currently available LDL-lowering

1 therapies to patients with familial
2 hypercholesterolemia or statin intolerance. Thank
3 you.
4 DR. SMITH: Thank you.
5 My understanding is that registered speaker
6 number 8 will not be speaking. So at this point,
7 will speaker number 9 please step the microphone
8 and introduce yourself? Please state your name for
9 the record and any organization you may be
10 representing.
11 DR. ZANGANEH: I'm Farhad Zanganeh. I'm
12 representing ACE, American College of Endocrinology
13 and American Association of Clinical
14 Endocrinologists. I'm the medical director of
15 Endocrine Diabetes and Osteoporosis Clinic in
16 Sterling, Virginia. I have no relationship with
17 Amgen, Regeneron, or Sanofi.
18 I was going to review what we know and what
19 we don't know, and I modified some of my
20 presentation to adapt to earlier discussions.
21 Inhibition of PCSK9 with monoclonal
22 antibodies is the most effective approach in

1 reducing LDL-C in people with non-FH, heterozygous
2 FH, and LDL receptor defects on statins, diet-alone
3 when added to existing therapy unable to treat
4 statins, ineffective doses of statins, and maximum
5 statins not tolerated. They have good data on
6 LP(a), and so far in large phase 2 and 3 programs
7 in 6,000 patients have had good data. And we have
8 larger studies ongoing.
9 So what about the statins? Statins are
10 amazing. Statins are king. Statins are so good
11 that I believe that they have prevented A1c and
12 diabetes studies to show any outcomes data. But
13 what is the problem? Patients cannot tolerate
14 them.
15 So I think the point is the games we play
16 clinically with patients is, have you been on
17 simva? Have you been on fluva? Have you been on
18 pita? Have you been on atorva? Have you been on
19 rosuva? Yes, I have. I have pain. My liver goes
20 up.
21 So I think the point is the statin
22 intolerant is not a mirage. People cannot

1 tolerate. What is the purpose of guidelines if you
2 cannot get to these guidelines? We are afraid of
3 people not using statins and jumping to these
4 others. Every move I make in my practice is
5 managed. Preauthorization is a term that kind of
6 shakes me, anything I have to do.
7 So I think the point is people realize that
8 the most data is with statins. And of course, what
9 happens to these patients that are not at goal?
10 They don't sit around. They look for other
11 therapies. They are on extended-release niacin,
12 which has more side effects. They're on LDL
13 apheresis, expensive. They could be on lomitapide
14 or mipomersen.
15 Then the point is life is expensive. I'm
16 sure you saw the cover of this week's Bloomberg. I
17 mean, this is the Hep C conversation. What is the
18 price on life? Life is expensive.
19 I'm not an economist. I'm not a politician,
20 neither one of any of you. I think the point is
21 innovation in science. I think the concept of this
22 class of drugs came out of need. The greatest of

1 innovations come out of need. When the complete
2 comes, the incomplete will go away. Data will
3 arrive in time. I think right now what we have is
4 LDL reduction in people that need it.
5 Also, I do agree we need outcomes data and
6 the days of surrogates are gone. But you heard
7 from patients earlier that some of the symptoms of
8 this disease goes beyond events. These cholesterol
9 plaques actually cause pain, cause blockage that
10 may be an independent entity than actual CV
11 outcomes.
12 So I think the point is that this story of
13 where these drugs will be plugged in is actually
14 every -- N of 1 is its own individual therapy, but
15 it would be on the foundation of statin, beyond the
16 highest dose of statins for patients that can only
17 take once weekly of something. And if you go
18 1 milligram over, they cannot tolerate it.
19 So I think the point is that these are the
20 real stories, and the only way that I know these
21 stories is because I always say the material
22 writers of my stories are the patients that I see.

1 This is where the real stories come through, and I
2 think nowhere else could we tell them better than
3 the people that spoke before me.
4 So again, as I mentioned yesterday, this is
5 not rite of passage, but what you have seen is
6 safety that is similar to ezetimibe, efficacy
7 better than statins.
8 Outcomes study are a must, but it should not
9 be -- these folks should not be held over for years
10 until the data arrives. I think that's the way
11 science advances, and I think until then, we should
12 just move forward with what we have. Thank you.
13 DR. SMITH: Thank you.
14 Will speaker number 10 please step up to the
15 microphone and introduce yourself? Please state
16 your name and any organization you are representing
17 for the record.
18 MR. JOHNSTON: My name is William Johnston.
19 I am here at the meetings as a consultant to a
20 European institutional investor. I have no ties to
21 Amgen or Regeneron or Sanofi that come with that
22 background.

1 I'm a former CEO of a biotech company. I
2 brought drugs to the marketplace. I believe I have
3 a reasonable understanding of the drug development
4 process. I also am an individual, and my maternal
5 grandfather died at 55 with a sudden heart attack.
6 My paternal grandfather died at 55 with a sudden
7 heart attack, as did my father.
8 I'm 70. I've not yet had a heart attack. I
9 went on Mevacor and had a prescription for Mevacor
10 the day after it was approved. I now take Zetia in
11 addition to the Mevacor. Prior to the availability
12 of those drugs, my total cholesterol was running
13 around 350. Two months ago, it was 121. I'm
14 fortunate, I'm a strong responder to the drugs.
15 We have five children and 13 grandchildren.
16 Four of our five children have familial
17 hypercholesterolemia. They inherited it from me.
18 Both of our daughters are intolerant to statins.
19 One of those daughters is a year from the age where
20 my mother had a heart attack.
21 For them, I appeal to you to
22 consider -- there doesn't appear, and you've

1 discussed it, a significant safety signal here.
2 There are obvious safety concerns and information
3 where we have inadequate data to make a final
4 determination, but there are people out there who
5 will die in the absence of having adequate drug
6 therapy.
7 I ask you to be considerate of those people
8 and follow the pattern that was followed for the
9 statins and for other drugs, where the surrogate
10 indicators were sufficient to go ahead and allow
11 those drugs to come to market.
12 While I was 55, every day I wondered, is
13 this the day that I will die, having had my
14 grandfather and my dad pass away. I don't want to
15 see my daughters go through that, wondering when
16 will this catch up with me. They need an
17 alternative to statins, and request that that
18 consideration be given them. Thank you.
19 DR. SMITH: Thank you.
20 Will speaker number 11 now please step up to
21 the microphone and introduce yourself? Please
22 state your name and any organization you are

1 representing for the record.
2 MS. AHMED: Good afternoon. My name is Cat
3 Davis Ahmed. Thank you for the opportunity to be
4 here today. I am the director of outreach for the
5 FH Foundation. However, I'm speaking today as an
6 individual with familial hypercholesterolemia, and
7 I have no direct financial relationship with any of
8 the sponsors.
9 I have FH. My father and his three brothers
10 all have FH. They were saved by early diagnosis
11 and treatment, although each has had an event,
12 including six bypass surgeries among them over the
13 last 35 years. My two sisters also have inherited
14 FH.
15 Untreated, my LDL is over 300, my LDL. I
16 worry every day. Mostly, I worry about my
17 daughter. My 10-year-old inherited FH from me, my
18 youngest. My perfect little dairy-free gymnast has
19 a total cholesterol over 300, which was discovered
20 when her pediatrician screened her. I work every
21 day to preserve her cardiovascular health.
22 At the FH Foundation, we work hard to change

1 the fact that 90 percent of people with FH don't
2 even know that they have it. I tell people every
3 day, FH is common, FH is life-threatening, FH is
4 under-diagnosed, and FH is treatable. But people
5 with FH, as we've heard today, need more treatment
6 options.
7 I hear from people who have had heart
8 attacks before they learned they had FH. They did
9 not even have a fighting chance to prevent their
10 heart disease.
11 Most of us expect that it is not if but when
12 we'll have a cardiac event. As grateful as we are
13 to have safe and effective treatments available
14 today, they are not enough for so many of us.
15 To quote Rhiannon from the FH Foundation's
16 Facebook discussion page where you'll find many
17 with FH, she says, "I want to do all that I can to
18 be here for my family as long as possible. Having
19 treatment options means hope for a longer life with
20 our loved ones."
21 I thank you for your consideration. Good
22 afternoon.

1 DR. SMITH: Thank you.
2 This panel appreciates the contributions of
3 all of the open public hearing speakers, and the
4 open public hearing portion of this meeting has now
5 concluded, and we will no longer take comments from
6 the audience.
7 The committee now will take up, I think, a
8 final review of some clarification questions and
9 will also start with some data that was requested
10 from the sponsor.
11 I ask the sponsor and the panel members to
12 seek to be as focused and as brief as you can,
13 covering the essential points to the extent they
14 really should be. But I want to make sure that we
15 have enough time to really focus on the discussion
16 questions and voting questions being asked by the
17 FDA because we can then be of the most assistance
18 to them.
19 DR. WASSERMAN: So slide up. Actually,
20 slide down. So the question that Dr. Smith and
21 Dr. Craig asked about the median exposure in the
22 phase open label, so that's study 138. The median

1 exposure is 9.3 months. So that means that
2 patients had six months to change their therapies
3 in that.
4 Just as a point of reference, you did ask
5 about the phase 2, and that's slide up. So this is
6 the phase 2. Now, you need to take this with a
7 very large grain of salt. We strongly discouraged
8 in the protocol any change of background therapy.
9 So I would not base any decisions based on this
10 data, but you did ask for it so I wanted to show it
11 to you.
12 But the phase 3 9.3 months, we continue to
13 monitor it obviously, and I can say anecdotally
14 that what I showed you for the phase 3 open label
15 has been consistent.
16 **Clarification Questions (continued)**
17 DR. SMITH: Thank you.
18 So we'll go to panelists now for clarifying
19 questions or points, and we'll start with
20 Dr. Budnitz.
21 CAPT BUDNITZ: Thank you. Dan Budnitz.
22 Just a couple quick clarifying questions for

1 Dr. Scott, I believe, on his slide 121 about the
2 comprehensive pharmacovigilance plan. I think
3 we'll be discussing the issue of detecting safety
4 signals from the current database of information,
5 which are largely short-term studies, and even the
6 long-term study looks like it hasn't been followed
7 for 7.4 months.
8 I'd like to hear just a few more details
9 about the postmarketing pharmacovigilance. In
10 particular, there's the notation, the second
11 bullet, about signal detection in various
12 databases. What are these databases you're talking
13 about? And in specific, will they be able to look
14 at dosing issues, in particular where we have very
15 little data on the proposed intensive dosing for
16 familial hypercholesterolemia?
17 Then also, a second question on the
18 neurocognitive safety follow-up study looking at
19 cognitive function, what is the time frame for
20 these kind of analyses? I think the concern being
21 not so much in the first 120 days but after two
22 years or three years

1 DR. SCOTT: Sure. Our intention is, after
2 launch, that we will follow various available
3 databases that are similar to the FDA Sentinel
4 database to look at signal detection, and we will
5 be looking at the pattern of use of evolocumab
6 looking at concomitant therapy, if that's the kind
7 of question you wanted to know.
8 CAPT BUDNITZ: So you will be able to link
9 to usage and what the dosage is going to be?
10 DR. SCOTT: Yes, yes. And that's standard
11 activity for us.
12 You asked about the Ebbinghaus cognitive
13 function study that we initiated in the FOURIER
14 study. So towards the tail end of recruitment to
15 FOURIER, we started enrolling patients into
16 Ebbinghaus in a blinded fashion, obviously,
17 patients in FOURIER who are having their cognitive
18 function tested.
19 We've heard discussion about what the
20 ability of cognitive function is to test for
21 differences. The cognitive battery has been
22 validated in a variety of different patient

1 populations. There's a lot of normative data, and
2 for instance, can tell that the difference -- can
3 pick up the change in cognitive function between
4 going from the age of 55 to 60.
5 So it's pretty sensitive. We think the
6 2,000 patients should give us considerable ability
7 to pick up any changes in cognitive function,
8 either on the positive side, because some of us
9 believe that reducing stroke and vascular disease
10 will improve cognitive function, or on the negative
11 side.
12 Did I answer all your questions?
13 CAPT BUDNITZ: And so that cognitive testing
14 takes place over how many years?
15 DR. SCOTT: It will take course over the
16 remainder of FOURIER, so it will be a couple of
17 years. We've stated that FOURIER will end not
18 later than 2017.
19 For full disclosure, I should tell you that
20 there is a possibility it could end as early as
21 later in 2016. So we'll have a couple years,
22 certainly a lot more data than we currently have.

1 DR. SMITH: Dr. Rosenberg.
2 DR. ROSENBERG: Thank you.
3 Some questions about adherence. I might
4 have missed it this morning, but could you produce
5 the data you have on adherence, especially in the
6 52-week trial as well as the follow-up study?
7 Given the data on adherence, you mentioned
8 that in the FOURIER trial, you have a large sample
9 size because you accounted for this issue as you
10 mostly drop out rather than drop in. So could you
11 review those data?
12 Finally, given levels of adherence or loss
13 of adherence of 20, 30, 40 percent, et cetera, and
14 the pharmacokinetics of the drug, what are these
15 different levels lack of adherence will have on
16 drug levels?
17 DR. WASSERMAN: So first, the question was
18 on adherence, and then the next question was around
19 the FOURIER powering about drop out, drop in. And
20 I might actually ask Dr. Sabatine to come to the
21 mic for that. And then the last question was
22 really around adherence and its level. Is

1 that -- okay.
2 So I think I can take the first and the
3 third questions, so slide up. This is the phase 3
4 study disposition, and you can see that the 12-week
5 studies all on the left all had greater than
6 95 percent adherence to the subcutaneous injection.
7 For the long-term study, you can see that it
8 dropped and that about 11.2 percent did
9 discontinue. You will note that the majority are
10 due to subject request, and as is not uncommon when
11 you have long studies, patients move.
12 In addition, during that study, we had a
13 formulation in which 6 mLs was delivered for the
14 monthly dose. And so we also think that that
15 desire not to have three injections of 2 mLs or
16 2 injections of 3 mLs may have contributed to that,
17 but that's just conjecture.
18 The next thing I'd like to show -- so in
19 terms of the adherence to the subcutaneous
20 injections, the data I'm going to show you in a
21 moment looks at our phase 3 studies. And during
22 the phase 3 studies, at the request of Drs. Craig

1 and Smith, we incorporated the patient
2 self-injecting at home and in the clinic under
3 observation. So the first month of these
4 three-month studies was in the clinic under
5 observation. The middle month was at home, so no
6 observation, no coaching, no nothing, just
7 completely hands-off. And then the last month was
8 again under observation.
9 Slide up. So what you're going to see is
10 monotherapy, combination therapy, statin intolerant
11 and heterozygous FH comparing the dark blue, which
12 is week 8, and the light blue, which is week 12.
13 And I think you can appreciate that there is not a
14 meaningful difference in patients who are injecting
15 at home with no supervision versus patients
16 injecting in the clinic with a study coordinator
17 observing.
18 Now I'll turn it over to Dr. Sabatine to
19 talk a little bit more about FOURIER.
20 DR. SABATINE: Thanks very much for the
21 question for FOURIER. If we can have slide up,
22 please.

1 This slide here shows an overview for some
2 of the power considerations, and so for the sort of
3 key secondary endpoint of CV death, MI or stroke,
4 the target is 1,630 events.
5 The way we came to that was first starting
6 with an ideal effect of the drug of a 20 percent
7 risk reduction. That actually was quite
8 conservative because given the LDL criteria, where
9 patients need to have an LDL above 70, we would
10 anticipate when we designed the trial that likely
11 the median LDL would be close to 100. Sixty
12 percent, then, reduction from that would then be
13 60 milligrams per deciliter, about 1.5 millimoles.
14 But when we designed this, we didn't have
15 the results of IMPROVE-IT, so we were deliberately
16 cautious in terms of what the effects of a
17 non-statin might be on top of a statin and what the
18 benefit might be as we started to plumb the depths
19 of lower LDL.
20 Then on top of that what's factored in is
21 about a 10 percent rate of sort of drop out or drop
22 in, considering this was an injectable and

1 long-term therapy, and we weren't sure how well it
2 would be tolerated.
3 So with all that calculated in, it's
4 actually well powered with about 90 percent power
5 to detect about a 15 percent risk reduction. And
6 also it's noted there the usual lag there for
7 treatment, which has been seen in some of the
8 statin trials.
9 As you well know, some of them have a lag of
10 two years. Others with more potent lipid lowering
11 have very small degrees of lag. And then you can
12 see the loss to follow-up rate.
13 Does that answer your question? Good.
14 DR. SMITH: Dr. Hiatt.
15 DR. WASSERMAN: I'd just like to make one
16 clarifying question, if I may. It's 10 percent per
17 annum, and then the other just really quick thing
18 is that the observed rate of that has been much,
19 much lower.
20 DR. HIATT: Just to follow up to that,
21 what's your p-value since it's first in class,
22 first entity? Are you at 0.05 or 0.01 or less than

1 that?

2 DR. WASSERMAN: It's 0.05.

3 DR. HIATT: And I'm assuming you have

4 interim analyses in the design --

5 DR. WASSERMAN: We don't have any interim

6 analyses in the design.

7 DR. HIATT: Zero?

8 DR. WASSERMAN: Zero.

9 DR. HIATT: Really?

10 DR. WASSERMAN: Really.

11 DR. HIATT: That's surprising.

12 (Laughter.)

13 DR. WASSERMAN: We have a DMC that's

14 monitoring. We feel that this data is very

15 important. We want to do it right, which is why I

16 think when we've talked about our assumptions,

17 we've been conservative. We want to get the

18 information that the community needs to address the

19 question that you've all been talking about.

20 DR. HIATT: But if you believe it's going to

21 be really, really effective, wouldn't it be ethical

22 to stop early if you have overwhelming efficacy?

1 DR. WASSERMAN: If our DMC decides that the
2 efficacy is that overwhelming, they can inform the
3 sponsor and let the sponsor know that they would
4 recommend termination of the trial
5 DR. HIATT: So you do have an interim
6 analysis?
7 DR. WASSERMAN: It's not a formal interim
8 analysis.
9 DR. ROSENBERG: For the question of
10 adherence, do you have any data from this type of
11 drugs that are administered every week or every
12 other week on what would be the long-term adherence
13 to such protocol? And what will be -- it was part
14 of my initial question -- the effect on LDL if the
15 patient was taking any other injection, for
16 example?
17 DR. WASSERMAN: I have to answer your
18 question on adherence a little circuitously because
19 we don't directly measure adherence except by
20 looking at LDL. So what I can tell you is when we
21 designed the program, we were concerned that this
22 is an injectable therapy, and unless you have a

1 cardiovascular event, it is asymptomatic. And we
2 were concerned about how patients would then adopt
3 and adhere to an injectable therapy.
4 As the FDA was well aware when we designed
5 our open label extension, we did not anticipate
6 75 percent of the patients in those studies rolling
7 over. We thought it was going to be significantly
8 less, like less than 30 percent. And that was
9 based upon other experiences that we've had with
10 injectable therapies for symptomatic diseases.
11 So for the patients, it seems that the
12 patients self-select to a degree. We did mention
13 that when we looked at the patients that rolled
14 over versus the ones that didn't roll over, they
15 tended to have slightly higher LDLs and slightly
16 higher cardiovascular risk. And the ones that
17 seemed to preferentially roll over the highest were
18 in the heterozygous FH population, the combination
19 therapy population, and the statin-intolerant
20 population. But obviously, if they stopped taking
21 the drug, their LDLs are going to back.
22 Then, I think you had a question -- and I'd

1 like you to clarify it, please -- about another
2 injection with it?
3 DR. ROSENBERG: No, it was a general
4 question -- I think you answered it -- about in
5 prevention, what will be the long-term adherence
6 with such an intervention. All the treatments that
7 are given like that in diabetes --
8 DR. WASSERMAN: Absolutely.
9 DR. ROSENBERG: -- for example, I wondered
10 if you had any knowledge of.
11 DR. WASSERMAN: From what we've seen to
12 date, the adherence has been well or good. I think
13 obviously time will tell. It is an injectable
14 therapy, and we do think that that will be, to a
15 degree, an impediment to some patients. To other
16 patients that are more motivated and are concerned
17 about their cardiovascular risk or have very high
18 LDLs or very high cardiovascular risk, they may be
19 more motivated to use an injectable therapy for
20 this condition.
21 DR. SMITH: Dr. Hiatt, to finish your
22 questions.

1 DR. HIATT: A quick clarifying question to
2 the sponsor. If you get a label for homozygous
3 patients -- I'm wondering how you're going to label
4 this because it was a little bit counterintuitive
5 when I first read the data that modulating PCSK9
6 would work in those patients, and it appears to do
7 so. But then also noted in the FDA background,
8 there's at least one patient that had no response.
9 So since we don't typically -- since these
10 are diagnoses that are more clinical than
11 genetically tested, is it just simply of an absence
12 of a reduction that will be in the label that you'd
13 stop the therapy and at what point in time and what
14 do you consider to be lack of a change and that
15 kind of thing?
16 DR. WASSERMAN: I appreciate you bringing
17 that up. Slide up. So I believe Dr. Wilson asked
18 this question a little bit earlier, and having some
19 time to kind of digest his question, we looked
20 at -- we did genotyping in our homozygous FH
21 studies as well as our heterozygous FH studies to
22 better understand how the genotype would

1 potentially impact function.
2 So in homozygous FH, if you are just -- you
3 can see that it's about 28 out of the 49 were
4 defective in both alleles, so had basically just
5 defective LDL receptor activity. And then the
6 other 21 percent were either not determined or
7 null, and that one null patient falls into that
8 bucket. And that one null patient clearly does not
9 respond. But there's other mutations that have a
10 little bit less of an effect.
11 Again, I think when we talk about the
12 homozygous familial hypercholesterolemia
13 population, in general, the clinicians that see
14 those patients are at specific centers where they
15 specialize in this. And indeed, there was a
16 comment on the availability of apheresis and stuff.
17 There's like something on the order of 40 centers
18 in the United States that are capable of doing
19 apheresis.
20 So for these patients, I think I'm less
21 concerned about the labeling. However, we are
22 committed to making sure that we work with the FDA

1 so that it's very clear to patients. But in
2 general, what I would say is that you can see after
3 one dose whether or not the patient's responding.
4 And obviously, if there is a desire to endeavor to
5 further suppress the PCSK9 to see if you can get
6 additional LDL lowering, we would support that
7 provided that we come to an agreement with the FDA
8 and this committee around the benefit/risk in that
9 population.
10 DR. SMITH: Was that a follow-up,
11 Dr. Shamburek? Okay. Dr. Nason.
12 DR. NASON: Coincidentally, mine actually is
13 kind of a follow-up, though it wasn't intended that
14 way. I was interested in the HoFH patients and the
15 question of the dosing, the once a month versus
16 once every 2 weeks.
17 If it's possible, to actually start with the
18 FDA's slide 24 because I thought that was pretty
19 interesting, that looked over time, broken down by
20 those who titrate or do not, and also those who are
21 apheresed and those who are not.
22 I just wanted to make sure I understand,

1 first of all, that the ones who are on apheresis,
2 were they sort of automatically started on the
3 2-week dosing?
4 DR. WASSERMAN: Yes.
5 DR. NASON: And everybody else if you were
6 not apheresis, you were started on the 4-week
7 dosing --
8 DR. WASSERMAN: That's correct.
9 DR. NASON: -- and then were given the
10 choice.
11 Do you have individualized data for those
12 people who do switch? Because that green line is
13 the people who start on the monthly and switch.
14 You folks commented that there was a 6 percent, I
15 guess, decrease between week 12 and week 24 there.
16 But obviously, there's some variability, and maybe
17 at week 4, they were lower and more similar to week
18 24.
19 As has been discussed, there are some people
20 maybe who respond better and some who don't. So I
21 don't know if you have any more data to sort of
22 fill that in a bit.

1 DR. WASSERMAN: I do. Slide up. This is in
2 study 271. These are patients that are obviously
3 not on apheresis, and in the study 271 protocol for
4 those patients at week 12, they were able to
5 up-titrate it if they wanted.
6 So you can see the 12 weeks of
7 420 milligrams every month gives you a 16 percent
8 reduction or about a 60 milligram per deciliter
9 decrease in LDL. And then 12 weeks of 420
10 milligrams every 2 weeks gives you a 22 percent
11 reduction or about an 81 milligram per deciliter
12 decrease.
13 You can see that it's a 6 percent decrease
14 overall, which is akin to the doubling of a statin
15 but in a non-homozygous patient. I believe -- and
16 Dr. Stein can correct me if I'm wrong -- that to
17 get this type of increase in a homozygous patient,
18 you have to triple the statin dose. Oh, quadruple,
19 sorry.
20 DR. NASON: So just commenting, it does look
21 like that 24 week is similar to where they were at
22 week 4. So I'm sort of wondering, I guess, about

1 individual variability in those, changes in those
2 responses.
3 DR. WASSERMAN: Sure. I actually like to
4 ask Dr. Stein to come up to comment on the
5 variability because it is something that we see in
6 homozygous FH in clinical trials.
7 DR. STEIN: Thank you. I think that's an
8 interesting question.
9 If we can have the slide up. So here's the
10 data if we look at according to the LDL receptor
11 status. So if you have a negative and no
12 LDL -- what is called LDL receptor negative or null
13 receptor -- you have virtually no LDL activity,
14 less than 2 percent, you will get no response to
15 these drugs because it works through up-regulation
16 of the LDL receptor.
17 If you have a single defective gene, which
18 you can see 28 out of the 41 patients did, you
19 actually get a much better reduction. And if you
20 have two defective genes, you actually get about a
21 47 percent decrease in LDL.
22 Fortunately, less than 5 percent of patients

1 are negative/negative. So if it's one in a
2 million, less than 5 percent of those one in a
3 million will have two negative receptors so it's a
4 very small majority.
5 About 70 to 75 percent of homozygous
6 patients will have at least one defective LDL
7 receptor gene, which gives them about 5 to
8 25 percent activity, and they get on average about
9 a 40 percent decrease in LDL. And then about half
10 of those will have two defective receptors of which
11 they will get close to 50 percent decrease.
12 I hope that answers your question.
13 DR. NASON: So you don't have any data
14 specifically with this antibody, then, like the 25
15 people who switched in that trial 271 --
16 DR. STEIN: I don't think we have the actual
17 genetic abnormalities in there, but that 6 --
18 DR. NASON: Or the LDLs over time, with the
19 switch on the individual basis?
20 DR. STEIN: The patients that were doubled
21 were more likely to be those who didn't respond
22 well, so they would be more weighted towards

1 patients with more severe defects.
2 The 25 milligram per deciliter reduction,
3 though, would translate -- if our reduction in risk
4 holds true for homozygotes -- to about another
5 10 percent decrease in cardiovascular risk.
6 DR. SMITH: Dr. Shamburek, you're next.
7 DR. SHAMBUREK: This is kind of in
8 reference. If you could bring up slide 43. Here
9 when you look at the PCSK9 levels, you show, I
10 think, at day 1, it's down 95 percent, and by
11 28 days, it's back to about 50 percent. And this
12 really is referring to the homozygous FH where you
13 had in your background mentioned that the levels
14 were 650 nanograms per milliliter, and the ones
15 getting apheresis were actually a little higher.
16 And the typical ones here are 200 to 300 nanograms
17 per mL less.
18 My question is do you have similar
19 information on the homozygous FH to see -- and
20 again, you don't have to have a slide because I
21 didn't ask, but do you see a similar 95 percent
22 loss and do you have 50 percent of same

1 pharmacokinetics dynamics in the homozygous FH? Or
2 are you only getting 80 percent or 60? Is that
3 part of the problem?
4 DR. WASSERMAN: I can show you. Slide up.
5 So this is data. These are PCSK9 values in our
6 titration analysis set. So these are non-apheresis
7 patients, and so you can see at baseline their
8 PCSK9 level is about 680 nanograms per mL. And
9 then after 12 weeks of 420 milligrams every month,
10 you can see how high they go back up to. It's 424.
11 If you give them the every 2 weeks, you can
12 see that we actually get their levels to almost
13 undetectable at 45 nanograms per mL. So it's just
14 goes -- I hope it goes to show you that --
15 DR. SHAMBUREK: So they seem to be rising
16 quicker because --
17 DR. WASSERMAN: They do. They have a lot
18 higher PCSK9, and they make it a lot quicker.
19 DR. SMITH: Dr. Sager.
20 DR. SAGER: Two questions. One is you were
21 going to show us -- I just wanted to remind
22 you -- the MACE graph. Also, I'm wondering does

1 the company have a position on how you would advise
2 physicians if someone's LDL gets extremely low,
3 let's say 10 or 15 milligrams per deciliter, or if
4 you have any viewpoint on that, I think it'd be
5 very helpful for the committee to hear that.
6 DR. WASSERMAN: Sure. I'm actually going to
7 have Dr. Marc Sabatine address both of those
8 questions
9 DR. SAGER: Thank you.
10 DR. SABATINE: If we could have the slide
11 with the Kaplan-Meier curve for the MACE endpoint.
12 So the MACE -- and by that, you meant the
13 triple -- we have those data. It's about
14 40 percent of the 60 or so outcomes we had in the
15 paper, and those are the cumulative incidence
16 curves there.
17 DR. SAGER: Thank you. And I understand
18 it's a very small data set, and we'll see when the
19 big study is done. But thank you.
20 DR. SABATINE: And then with regard to
21 patients who get very low LDL levels, I mean, as a
22 clinician, I would say congratulations. The data,

1 I think is certainly quite compelling for LDL down.
2 And we saw even in JUPITER, for those who started
3 less than 60 going down to less than 30, that they
4 benefited.
5 So I think once individuals get down to that
6 range of even less than 30, and so assuming in that
7 group it's kind of the 20 to 30 range that they had
8 the same degree of benefit. Slide up, please, just
9 to remind people of that.
10 Then other speakers have talked about Brown
11 and Goldstein, and so in their acceptance speech
12 for the Nobel prize, they commented that a
13 circulating level of LDL of around 25, 25 to 50 is
14 probably actually what the body is kind of designed
15 for and you don't need anymore.
16 I think in those cases, I think all that is
17 actually good news. We don't have data that
18 there's any down side. And then the other thing to
19 think about is that the homozygotes are or people
20 who at least are least compound hets. For PCSK9
21 loss of function, their LDLs are in the teens.
22 There's not a lot of them there, but they appear to

1 be healthy.
2 So as a clinician, I would say that if a
3 patient contacted me with that, as long as they're
4 doing well, I would say, great, we don't have any
5 data to suggest differently for now.
6 DR. SAGER: So there's no lower level that
7 would strike concern for you?
8 DR. SABATINE: So far we haven't seen a
9 level that's been of concern through this mechanism
10 until, obviously, larger databases will give us
11 more confidence for that, but so far, no, not that
12 I've seen.
13 DR. SMITH: Dr. Thomas.
14 DR. THOMAS: It ends up being a follow-up a
15 little to Dr. Sager by coincidence. I think the
16 guidance is important, and what I wanted to know is
17 the following:
18 In your trials, you excluded people with
19 LDLs less than 80. And it's quite possible in
20 clinical practice patients may be put on this drug
21 with LDLs in the 70s. So the potential for having
22 low LDL cholesterol is probably more if the

1 reduction is similar to what you've shown.
2 Are there any other dosing regimens that you
3 didn't present that may have a lower LDL reduction?
4 For example, you showed the 75 milligrams every
5 2 weeks and you had a significant LDL reduction,
6 but you had a lot peaks and troughs.
7 So I was wondering if you had any other
8 types of dosing regimens you might have done in
9 earlier studies for dose finding that have a stable
10 level without peaks and troughs but a lower
11 reduction in LDL.
12 DR. WASSERMAN: Your question's an
13 interesting one. The challenge is that PCSK9 is
14 something that your body constantly makes, right?
15 And as you give a monoclonal, at doses in our hands
16 of greater than 70, you basically knock it down
17 100 percent or to undetectable levels.
18 It's just then after that, you don't get
19 additional LDL reduction. You just get -- you
20 prolong the LDL reduction. And so if there's a
21 concern over low LDL, after 70 milligrams if you
22 measure your LDL, it will be as low as it can go.

1 And so if the concern is over low LDL, a half dose
2 doesn't get you there.
3 So when we were thinking about this
4 program -- slide up -- this is data that we
5 used -- this is our phase 2 dose ranging data that
6 really informed kind of how we were thinking about
7 the program and bringing it forward. And a lot of
8 it's based on the notion of lower is better, but
9 it's also we're very consistent with the current
10 ACC-AHA guidelines of high intensity versus
11 moderate intensity.
12 So what we did in our phase 2 studies -- and
13 remember, this is 1300 patients in dose ranging
14 studies -- we looked at the 140 milligram every
15 2 weeks, and on the bottom, versus the
16 420 milligrams every month. And I think you can
17 appreciate that the mean difference there is about
18 zero.
19 If you go to a lower dose such as the
20 420/280, the difference there is about 7 percent,
21 but you saw how much variability there was. And
22 then lastly, if you go to the 140 versus the 70

1 every 2 weeks, there's about a 20 percent
2 difference there. That 20 percent difference is
3 exactly what we saw in TNT in terms of the LDL
4 reduction difference between atorvastatin 10 and
5 atorvastatin 80.
6 So then the question really goes about, so
7 who's going to get these therapies? It's our
8 opinion, and it's the sponsor's opinion, that this
9 therapy should be used in patients who need
10 additional effective LDL reduction after statins.
11 So these patients all need to go through statins
12 first. If they need modestly effective additional
13 LDL reduction after that, ezetimibe is a wonderful
14 therapy.
15 But for patients with FH or the ones that we
16 studied that are statin intolerant that are very
17 far from getting control, this is an option. In
18 addition, for your high-risk cardiovascular patient
19 who you are concerned about, this is an option.
20 So again, it boils down to the benefit/risk
21 equation. With the patients that I'm talking
22 about, it's clear that the risk, it's very real.

1 If you don't treat these patients, they will have
2 heart attacks and strokes.
3 Then we have our safety profile that, I
4 think, we've all kind of seen, and we haven't
5 identified a major safety issue, as of today, that
6 would offset the predicted risk of that LDL
7 reduction. So when we were looking at developing
8 our program, that is why we did not choose to
9 pursue a lower dose.
10 DR. THOMAS: But what you've said, does that
11 mean you would think that if someone had an LDL
12 cholesterol of 70 or 65 and still was at high risk
13 if they'd had an event or active coronary syndrome,
14 you would recommend using Zetia over this agent?
15 DR. WASSERMAN: Well, so I'm actually going
16 to ask someone who's actually currently practicing
17 versus what I did or what I would have done. So
18 Dr. Sabatine -- or actually, Dr. Ballantyne.
19 DR. BALLANTYNE: I would, once again,
20 individualize a patient -- Christie Ballantyne from
21 Baylor College of Medicine. So the question
22 specifically -- could you repeat the question

1 again, exact patient profiles?
2 DR. THOMAS: So if you had a patient who had
3 an LDL cholesterol which was lower than the entry
4 guidance, so less than 80, so 70 or 65, and they
5 were high risk, and you felt that they needed
6 additional LDL lowering, from the JUPITER setting,
7 which isn't exactly comparable, would you -- based
8 on what I just heard, the suggestion sounds like
9 you might use Zetia over using this agent.
10 DR. BALLANTYNE: So I think if you're
11 talking with LDL at 70 and you've got
12 ezetimibe -- remember, using these agents, I would
13 imagine the same thing. Even if you're prescribing
14 Zetia lately, have you seen what the co-pays are
15 for your patients?
16 People like to think the FDA decides who
17 gets the drugs. It's not. It's the payers decide
18 who gets the drugs. And there's another control
19 mechanism here.
20 So yes, ezetimibe, particularly it'd be
21 generic in another year and a half, is going to be
22 your first choice for that type of a patient.

1 I think what you ought to look at is the
2 issue that comes up when we talk about FH versus
3 just high-risk CHD, not a target, remember, as was
4 pointed out about the diagnosis of FH, it's not
5 diagnosed very often. And what you usually have is
6 someone in your office who's on a high intensity
7 statin and their LDL is 115.
8 Now, do a little math. If the LDL has gone
9 down 50 percent on that statin, that means it was
10 over 200, and most probably even though you don't
11 have a diagnosis, they have some type of either
12 monogenic or polygenic disorder with it.
13 So I think there is this concept of not
14 pigeonholing something to just FH, is that if
15 someone has a high-risk patient who has a high LDL
16 on maximum tolerated therapy, their benefit is just
17 the same, and most likely, they have a genetic
18 condition. We just don't have a diagnosis.
19 For those of you who've looked at some of
20 these old criteria, Simon Broome and things, most
21 patients don't have the same kind of xanthomas
22 anymore with it.

1 DR. WASSERMAN: Dr. Thomas, let me just try
2 to also just put in my two cents. I think it's
3 going to depend on the patient. At the end of the
4 day, what we're committed to do is working with the
5 agency to make sure that we have a label that
6 allows the patient [sic] to do what they think is
7 right for the patient that's in front of them.
8 So if it's a 65-year-old male who just had
9 his third heart attack, and his LDL is 70 on
10 atorva 80 or whatever you want, it needs to be an
11 option for that clinician to decide is the
12 benefit/risk for this patient right.
13 Every clinician's different. Some are
14 always going to want the hard outcomes data and
15 will choose Zetia, and that's fine. But the
16 doctors and the patients need to have that
17 discussion and need to have those options.
18 DR. SMITH: Dr. Cooke.
19 DR. COOKE: The proposed indication for
20 homozygous FH is for its use in combination with
21 other lipid-lowering therapies. Is there any
22 experience with its use with the ApoB or MTP

1 inhibitors?
2 DR. WASSERMAN: We have not studied it with
3 those agents at this time.
4 DR. SMITH: Dr. Albrecht.
5 DR. ALBRECHT: Thank you. Actually, my
6 questions related to compliance and genotyping have
7 been answered. Thank you.
8 DR. WASSERMAN: Can you repeat the question?
9 What would you like to know?
10 DR. SMITH: There's no question.
11 Dr. Orza.
12 DR. ORZA: This is for the sponsor. In
13 discussing slide number 117, which was part of a
14 series of really helpful slides, you mentioned the
15 number needed to treat. And I was hoping that you
16 had the number needed to treat and the number
17 needed to harm for the HoFH population, the HeFH
18 population, and perhaps the statin-intolerant
19 population.
20 DR. WASSERMAN: I'll ask Dr. Rob Scott to
21 come to the microphone.
22 DR. SCOTT: So firstly, let's talk about the

1 statin-intolerant ones because I think that's the
2 easiest part. So for statin intolerant, this
3 equation is appropriate for statin-intolerant
4 patients. You can think about their baseline risk
5 based on their NCP risk category or the risk
6 calculator that's used and use the same
7 calculation.
8 So for patients with statin intolerance, it
9 depends on their baseline risk. It depends on
10 their baseline LDL. But I would say to you that
11 plugging in our own numbers in here, the average
12 LDL for our statin-intolerant patients was at 190.
13 So the 63 percent risk reduction seems
14 reasonable to consider in that regard, but those
15 patients could be at a variety of different
16 background risk. But it would seem to be an
17 appropriate therapy for anybody with moderate risk
18 and above for statin intolerant.
19 For heterozygous FH, actually the guidelines
20 do not recommend the use of the risk calculator.
21 And the reason for that is you can measure the
22 10-year baseline risk for a patient with

1 heterozygous FH and come up with a particular
2 number, but the reality is that the lifetime risk
3 for males is very close to 100 percent, and for
4 females, it's over 80 percent.
5 So the guidelines do not recommend the use
6 of the calculator in patients with FH. They
7 recommend aggressive treatment as soon as the
8 patient is diagnosed, if that answers your
9 question.
10 DR. ORZA: I was hoping to see maybe at
11 least for the HoFH population a number needed to
12 treat and a number needed to harm kind of side by
13 side.
14 DR. SCOTT: I could ask Dr. Stein to come up
15 and comment on that, but I would say that it would
16 be better than the patients that are in the far
17 left-hand corner, so the 5.
18 For the number needed to harm, it's
19 difficult to say at this stage because with the
20 data that we have, we've not identified any
21 specific harm. So it's difficult to plug a number
22 into there. You'll just have to accept that until

1 we have the outcome data, there may be some
2 uncertainty around that. But we don't have a
3 specific harm for this drug that we can plug into
4 that calculation.
5 DR. SMITH: Dr. Wilson.
6 DR. WILSON: When this advisory committee
7 reviewed the data for lomitapide and mipomersen, it
8 came to light that some of the patients taking
9 those products had very significant improvement in
10 their tendinous xanthomas. We haven't seen any
11 information on that so far.
12 DR. WASSERMAN: So I have anecdotes from
13 some of our sites and investigators that they have
14 seen in their FH patients, both homozygous and
15 heterozygous, regression of tendinous xanthomas. I
16 don't have pictures. I'm sorry.
17 DR. WILSON: Can you make any estimate,
18 though? For instance, out of people with high
19 cholesterol who have tendinous xanthomas, are 5 out
20 100 or 1 out of 100?
21 DR. WASSERMAN: I can't speculate. Again,
22 it's not something that we got in the case report

1 form. So the only way I get this feedback is I
2 have an investigator call me and say, has anyone
3 else reported this? I have a few anecdotes of
4 that.
5 DR. WILSON: That relates a little bit back
6 to Eileen Craig's talk about the duration. So your
7 experience is largely focused on 12 weeks, but you
8 have some out to 52 weeks. So you're marginal in
9 terms of being able to ascertain that.
10 Is that fair to say because of the duration
11 of exposures?
12 DR. WASSERMAN: So the duration of exposures
13 that you're talking about are the double-blind
14 placebo-controlled trials, and so you are correct
15 in that we have done the bulk of our primary
16 hyperlipidemia and mixed dyslipidemia studies that
17 way. That being said, we had these two large
18 open-label studies which patients were eligible to
19 roll over.
20 I do want to note to the panel, the reason
21 that the studies were designed that way when we
22 initiated the program is, again, going to the

1 question I think that Dr. Rosenberg brought up,
2 which is we were going into new unchartered
3 territory in terms of injectable therapies for an
4 asymptomatic disease until you have an event, and
5 we weren't sure what was going to happen in terms
6 of those studies. So we were, I would say,
7 cautious when we first endeavored to do that.
8 In terms of homozygous, I will show you from
9 the core deck -- slide up -- this is the overall
10 exposure for homozygous familial
11 hypercholesterolemia. I would say that we have one
12 of the largest databases right now of homozygous FH
13 patients in a clinical trial. We do have patients
14 that are out to two years.
15 So again, your point is well taken, but I
16 can't comment other than to say we do have
17 long-term data. It is in an open-label setting.
18 However, in the homozygous condition, I think that
19 that's warranted.
20 **Questions to the Committee and Discussion**
21 DR. SMITH: So there being no further
22 clarifying questions from the committee, I think

1 we'll now proceed with the questions to the
2 committee from the FDA and the associated panel
3 discussions.
4 I'd like to remind public observers that
5 while this meeting is open for public observation,
6 public attendees may not participate except at the
7 specific request of the panel.
8 So if we could project question number 1. I
9 will read this. Discuss the safety of evolocumab
10 as observed in the clinical development program,
11 and in our discussion, comment on the following:
12 A, discuss your interpretation of the safety
13 data with respect to any adverse effects related to
14 diabetes, liver-related safety, muscle,
15 neurological, neurocognitive events,
16 hypersensitivity as well as any other concerns you
17 may identify.
18 B, discuss the adequacy of the current
19 clinical database to characterize the safety of
20 evolocumab. Consider the extent of drug exposure,
21 i.e., number of patients and the duration of
22 exposure; the strengths, limitations of the study

1 designs themselves, and the generalizability of the
2 trial populations to the target patient populations
3 if approved.
4 C, discuss your level of concern regarding
5 the safety of achieving very low levels of LDL-C
6 induced by evolocumab.
7 What I would like to do is first and
8 together, discuss A and B and not C, know that
9 we're going to come to that later. I think that's
10 an effective way to divide this. So this is open
11 for discussion, comments.
12 Dr. Sager, I see your hand.
13 DR. SAGER: The overall database is pretty
14 robust. There aren't as many patients as maybe
15 we'd like to see who are very high cardiovascular
16 risk, but in terms of evaluating for safety, I
17 think that we see that there is potential for some
18 weak signals in pancreatitis, hypersensitivity,
19 diabetes, and maybe muscle and musculoskeletal.
20 I think that having this 27,000 patient
21 outcome study, the rest of the studies that are
22 going to be done, including the one looking at

1 cognitive function, the pharmacovigilance that the
2 company's planning as well as the pharmacovigilance
3 plans that the FDA, I'm sure, will put into place,
4 I think they're really going to be satisfactory to
5 bring those out.
6 So I don't feel that these are major issues
7 as we evaluate this today, but there are things
8 that need to be further looked at. And it's not
9 surprising that all questions can't be resolved at
10 the end of phase 3.
11 DR. SMITH: Dr. Thomas.
12 DR. THOMAS: I think I'll just break it
13 down. In the FH group, I actually think we're
14 fairly well off because this is a large study in
15 that population. So I don't have much concerns
16 about that.
17 I do have a few concerns about the overall
18 database. Most of the studies are 12 weeks long,
19 and I think, usually, you'd like to have a longer
20 period of time to assess safety. It really is time
21 on drug versus the placebo that people who aren't
22 on it, and 12 weeks is a little short to pick up, I

1 think, some of these concerns that we might have.
2 There's only the one trial that's 52 weeks,
3 but it's a smaller number of subjects. So I don't
4 think you can relate those to the 12-week studies.
5 The open-label studies, as the FDA mentioned
6 in their presentation today, Dr. Craig said, there
7 are limitations. There's self-selection. You've
8 got people who tolerate the drug who have an
9 invested reason to be on it. In an open-label
10 extension, you lose the power of randomization to
11 some degree even though you've randomized the
12 people who enrolled.
13 So I'm a little uncomfortable with the fact
14 that we don't have longer trials for the safety
15 assessment. I think if we had a few more of those,
16 that would actually help. There is no obvious
17 safety signal that's there that's concerning, but
18 in respect to the duration of most of the trials, I
19 think we can't completely answer that question.
20 DR. SMITH: Dr. Blaha.
21 DR. BLAHA: Hi. Mike Blaha. So I agree
22 with the limitations that were just stated. And I

1 think that there are some limitations to the
2 database, but in other ways, the database is quite
3 reassuring. And I'll kind of reiterate some of my
4 thoughts from yesterday and say that, overall, I'm
5 very impressed and somewhat reassured by the lack
6 of a safety signal for such a potent drug, and I
7 think that's quite reassuring in general.
8 With regard to diabetes, I'll say that I
9 think this is starting to emerge as a little bit of
10 a -- I don't want to call it a class, but I guess a
11 mechanistic effect. I think we're going to see a
12 lot of lipid lowering -- at least those that work
13 through the LDL receptor -- cause a little bit of
14 diabetes perhaps, and we'll all as clinicians get
15 used to talking to our patients about that. But
16 the benefit would seem to far out exceed the risk
17 in most patients. So in general, I'm quite
18 reassured.
19 DR. SMITH: Dr. Hiatt.
20 DR. HIATT: We're being asked to make a
21 decision today on the approvability of this drug
22 for rather a potentially broad utilization with a

1 database that has a relatively few number of
2 patient-years' total exposure. I agree with the
3 panel that not much has turned up of concern.
4 I'd also think that if the large outcome
5 trial had some major signal of concern, the data
6 monitoring committee would have alerted the sponsor
7 who would have alerted the FDA that something
8 concerning was going on.
9 That said though, if you're asked to assess
10 risk and benefit with the amount of exposure today,
11 it doesn't help assess the risk side in terms of
12 certainty of lack of a problem. That remains a
13 concern for me.
14 DR. SMITH: Dr. Burman.
15 DR. BURMAN: Thank you. I agree with the
16 comments that have been noted, but also think the
17 populations should be expanded to include more
18 minorities, older individuals, and also there's no
19 information regarding patients who are sick in the
20 intensive care unit, have other comorbidities, or
21 as noted before, patients who may become pregnant.
22 Certainly, longer-term studies are needed.

1 DR. SMITH: Dr. Rosenberg.
2 DR. ROSENBERG: So in terms of overall, I
3 feel we're in good position to evaluate the
4 benefit/risk of the drug and that larger studies,
5 especially short-term, would probably not give us
6 much more.
7 We needed many years and many tens and
8 hundreds of thousand patients on statin therapy to
9 start seeing some effects such as incidence of
10 diabetes, potentially cognitive function.
11 So it's not because we will have a few more
12 thousand patients that we'll be able to answer
13 those questions, but it is obvious that we'll need
14 to follow up those drugs very carefully both in the
15 controlled trials as well as observational studies.
16 DR. SMITH: Dr. Shamburek.
17 DR. SHAMBUREK: I would concur with them.
18 The one thing is, is I think there was not as many
19 of the high risk patients that we would see.
20 Certainly, the other groups are important, and
21 maybe down the line when we know outcomes, those
22 will be groups we want to target.

1 The other comment I'll just say is on the
2 initial studies, we had four 12 week and the one 52
3 week. And perhaps the amount of data we have for
4 the 420 Q monthly is limited because basically in a
5 12-week study, you're giving three doses and that's
6 it. So we're seeing four of the studies on three
7 doses, so in the Q monthly.
8 DR. SMITH: Dr. Wilson.
9 DR. WILSON: Just to build on what the
10 others have said, I think the group to especially
11 focus on, as was mentioned, high-risk but
12 especially heterozygous FH for more safety data.
13 We are just lacking on this. Where are the
14 26-, 52-week data for heterozygous FH? Those
15 patients, it looks like they're going to get 50
16 percent lower, and the homozygotes are 25 percent
17 lowering. They could really benefit, and that's
18 where we really want more information.
19 DR. SMITH: So I'll try to summarize, and
20 again ask the panel to help me out and add any
21 corrections to this as well.
22 So what we heard panel members express is

1 the opinion that there's a level of reassurance in
2 regard to potential -- in regard to the safety data
3 in that there have been no evident particularly
4 concerning signals.
5 But we also have heard multiple panel
6 members express the opinion that the database,
7 while robust in some ways, is, in fact, not an
8 adequate database to comfortably evaluate safety
9 and to be assured that there is not or will not
10 appear a safety problem.
11 The reasons for that have to do with the
12 overall numbers, which are still modest in
13 comparison with what one likes to see with safety
14 trials. There's a limitation in that the exposure
15 time of individuals is also quite limited with the
16 recognition that safety problems might be
17 unanticipated and might appear only after a long
18 period of exposure. And we're talking about a drug
19 in which the use may extend over many years.
20 There's note made also that there are
21 particular groups that different panel members
22 expressed concern about where they would

1 particularly like to know more safety data. And in
2 one direction where that goes is towards groups
3 that are not represented, or represented
4 extensively, within the available trial data. And
5 that includes, for example, members of races that
6 are present only in small numbers.
7 So again, one does not know with confidence
8 that safety problems would not occur that might be
9 evident in a subgroup such as those and not evident
10 in the more represented groups.
11 Then also, the concern was raised about
12 patients who might have intercurrent illnesses,
13 which might represent a different vulnerability to
14 safety problems that again are not assessed by the
15 data that are available.
16 Then the point was also made that in kind of
17 ranking what one would like to know that especially
18 for patient groups such as heterozygous FH or
19 homozygous FH, where there's a strong need and one
20 would anticipate extensive use that one would
21 particularly like to know more from all these
22 angles I've described in terms of numbers and

1 duration of exposure to be comfortable about
2 safety.
3 At the same time that it was noted that
4 there are no particularly concerning safety
5 signals, nothing as a scary immediate safety
6 signal, that there are some signals specific ones,
7 that one would like to focus on in further
8 evaluation and data, and that includes -- not
9 necessarily totally inclusively, but that includes
10 diabetes, pancreatitis, possibly some
11 muscle-related questions.
12 One might also add to that just the issue of
13 long-term exposure to a monoclonal antibody over a
14 long period of time.
15 So would anyone from the panel like to edit
16 that, additions or subtractions? Yes, Dr. Thomas?
17 DR. THOMAS: I think that your summary is
18 fine, but I didn't mention when I spoke, and I
19 think just to make it more explicit, in the 52-week
20 study, many of the patients that are in that study
21 probably would not be treated with this type of
22 agent because their cardiac risk is lower.

1 So we have much less data on the people who
2 would be the intended population outside of FH or
3 FH heterozygotes, people at high risk. And I think
4 that is a limitation. You really want to see the
5 data in the people who would actually receive the
6 drug if it was approved.
7 DR. SMITH: Any other comment?
8 (No response.)
9 DR. SMITH: So I think we'll go to part C of
10 question 1. So again, what this is, it's to
11 discuss the safety of evolocumab as observed in the
12 clinical development program and comment on your
13 level of concern regarding the safety of achieving
14 very low levels of LDL-C as induced by this agent.
15 Dr. Hiatt.
16 DR. HIATT: This question is identical to
17 the one yesterday with the drug name changed. And
18 the reason I mention that is I think that if
19 approved, how do you inform physicians to prescribe
20 this, particularly around this, what's the lower
21 bound is a tough one because there's very sparse
22 data. And the way to answer that question

1 definitively is to understand both the risk and the
2 harms at a very, very low LDL cholesterol level.
3 Since not a lot of patients will be
4 achieving those levels, there will always be a fair
5 amount of uncertainty. I realize there's no
6 theoretical concern, I suppose, to go that low, but
7 I'm not satisfied by theory as I am by actual cases
8 and events of both risk and benefit to help inform
9 us.
10 So I think that physicians should be given
11 some guidance, and yesterday we asked what would
12 that number be. I don't know. Maybe it's
13 25 milligrams and less, but there has to be
14 something. And until you know more.
15 I think this also gets to a later question,
16 which is about titration, dose titration. This is
17 kind of a fixed dose thing, and other issues will
18 come up in a minute about that.
19 But I'm a little bit worried. If you're
20 down at 20 and you sort of want to do something
21 about that, and your job, you can either start or
22 stop the drug, then what you're going to probably

1 do is change something else, and that may not be a
2 good idea.
3 So I think the sponsor should probably think
4 about how to inform physicians with what the
5 information you have is now and also may want to do
6 some additional studies on dose ranging to try to
7 get a better handle on how physicians can use this,
8 and particularly using maybe lower doses if that
9 was deemed appropriate in a select number of
10 patients.
11 DR. SMITH: Dr. Burman.
12 DR. BURMAN: Thank you. I don't think
13 there's any compelling evidence that a lower LDL
14 concentration is detrimental as compared to a
15 so-called normal LDL level, at least based on data
16 that we are aware of today.
17 As we mentioned, about 50 percent of
18 patients with an MI have a normal range of LDL.
19 Babies are born with an LDL of about 40 to
20 70 milligram per deciliter. And multiple studies,
21 including the JUPITER study, suggested that a lower
22 LDL below the so-called normal range might be

1 beneficial.
2 Evidence suggests that a lower LDL is
3 associated with few cardiovascular events. It can
4 include epidemiologic data against different
5 cultures, clinical trial data such as the JUPITER
6 study, genetic disorders such as PCSK9 deficiencies
7 that have actually been beneficial.
8 Statins have similar mechanisms of action as
9 PCSK9 inhibitors, so it gives us some hope that
10 they'll have similar beneficial effects on
11 cardiovascular events.
12 However, I'd emphasize the degree of
13 therapeutic intensity should depend on the
14 patient's risk for cardiovascular disease, and the
15 duration of decreases in serum LDL also will likely
16 play a role in the extent of effect.
17 I do believe longer-term studies assessing
18 low LDL levels should be performed, and I do have
19 some concern that CRP isn't decreased with these
20 medications. And of course, I take into
21 consideration the previous studies where lowering
22 LDL did not correspond with long-term benefit. But

1 all in all, I believe at present, there is no known
2 harm to a low serum LDL.
3 DR. SMITH: Dr. Rosenberg.
4 DR. ROSENBERG: I'll be brief because
5 everyone has said what I wanted to say much more
6 eloquently.
7 Both from today and from the literature with
8 statins and the other LDL-lowering drugs, there's
9 no really evidence at the level at which we start
10 harming patients unless we go -- we are in very
11 low, but we agree until now, a newer way of getting
12 exact low or the studies you mentioned, the
13 emerging studies, and studies of native
14 populations, does find that this maybe normal level
15 is really low.
16 So from a public health perspective, we're
17 concerned about high levels, low levels that should
18 be studied, but that's not something that I'm
19 really concerned of.
20 DR. SMITH: Dr. Budnitz.
21 CAPT BUDNITZ: I agree, based on the data,
22 as other folks have said, there are not compelling

1 data that say low levels are harmful, but want to
2 reemphasize that, actually, we really just do have
3 a paucity of data still. Even though there might
4 be, I guess, in the study 1500 folks with LDLs less
5 than 40, this really is over a very short treatment
6 time, this one-year control open study but really
7 average time of seven months.
8 So as Dr. Hiatt talked about, we used these
9 data to look at what the upper level of harm might
10 be. And when we look at the data of new onset
11 diabetes, there's an absolute increase of 1 percent
12 over placebo, and that's like 1 percent over
13 approximately a six-month period, and these folks
14 will be on these drugs for longer and longer.
15 If you're on this drug for 10 years, now you
16 have an absolute increase of 20 percent if you
17 accept that kind of limited point estimate that we
18 have for this limited data.
19 So I think I'm concluding where the folks
20 are that -- and agree with Dr. Burman that
21 longer-term studies are needed, but I want to
22 emphasize that our data set at this point is quite

1 small.

2 DR. SMITH: Dr. Sager.

3 DR. SAGER: I would echo that. And also, I

4 share some of Dr. Hiatt's concerns, too, in that

5 maybe extremely low is just absolutely fine, but

6 there's lack of data, and maybe it isn't actually

7 okay.

8 On the other side, we don't have real

9 evidence that, let's say, having an LDL-C less than

10 40, there's not much data that that actually

11 necessarily supplies much benefit. I think the

12 JUPITER study is hard to extrapolate from. It's a

13 very different population, those individuals with

14 high C reactor proteins which this population in

15 these studies obviously didn't have. That was kind

16 of a very specific population. And the cut we saw

17 was less than 70. We didn't see a cut for less

18 than 30 or 20 or 10.

19 So it's a real conundrum. I don't know what

20 the right answer is. It's very difficult. It'd be

21 great to have this study so there could be some

22 data. I think I'm very certain that there's a lot

1 of uncertainty.

2 DR. SMITH: Dr. Wilson.

3 DR. WILSON: Just a simple point because

4 there are lipidology guidelines in the pediatric

5 age group, and I think my colleagues in pediatric

6 endocrinology will agree. There's a fair amount of

7 caution before age 8, especially in the first four

8 years of life. So if a heterozygote was diagnosed,

9 we actually go fairly carefully with statin use and

10 should be in the hands of experts in the pediatric

11 age group.

12 I'm not sure if there's any movement yet for

13 an indication in a pediatric age group, but it is

14 definitely different as brain is developing and we

15 need neuronal development with fats and some

16 element of cholesterol. Perhaps they could weigh

17 in on what they might recommend.

18 DR. COOKE: With a caveat that I don't do a

19 lot of treatment for this, there is a lot of

20 caution in the younger children, but there is a

21 growing body of literature of relatively aggressive

22 statin use with the heterozygous FH patients with

1 no safety concerns being demonstrated. So there is
2 caution, but there hasn't been anything alarming
3 that's turned up.
4 DR. SMITH: Dr. Blaha.
5 DR. BLAHA: I want to reiterate a few of my
6 comments from yesterday. I'll mention, of course,
7 that there are measurement issues -- and there are
8 other measurements experts in the room -- of
9 measuring low LDL cholesterol. And certainly with
10 the Friedewald equation versus a direct
11 measurement, you can get an underestimate of one's
12 LDL at the low range. So perhaps the LDLs that
13 we're seeing that are low aren't quite as low as we
14 think. But still that doesn't mitigate my level of
15 concern.
16 I don't think anyone in the room would say
17 they have no concern. I don't have a high level of
18 concern based on the combination of genetic,
19 biologic, mechanistic data, but I certainly have
20 some concern and certainly long-term data is
21 needed.
22 But the idea of a measurement of low

1 cholesterol is a call to action for all of us to
2 think about to make sure that we are accurately
3 quantifying low LDL cholesterol.
4 DR. SMITH: So I will endeavor to summarize.
5 So we've heard panel members express, on the one
6 hand, concern that there is really not enough data
7 to answer the question of whether or not very low
8 levels of LDL-C might, in fact, be a safety
9 concern. And there also is not enough data
10 available from the literature to really address
11 that question.
12 We've heard a little bit divergent views in
13 that one may find some data that argue that it's
14 not a major worry, but we also -- the data really
15 are not satisfactory in terms of other studies. So
16 it remains an open question.
17 It's not, I think, by the committee in
18 general been expressed as a major concern. In
19 other words, they're not alarm signals or there's
20 not information available from the literature
21 elsewhere that raises as a major concern. But it's
22 really not adequately addressed by what's known,

1 and so it's very important to obtain more
2 information as we go forward.
3 Again, that is information in terms of broad
4 numbers of patients where problems might be
5 identified and emerge, and it's also information
6 derived from long-term treatment and thus long-term
7 exposure to very low levels of LDL-C. And both of
8 those are things that one would like to evaluate
9 with further data as things go forward.
10 There may be special issues in younger
11 children, and there's a background of concern about
12 how aggressively lipids should be lowered in young
13 children who are developing multiple tissues,
14 including central nervous system tissues. But over
15 time, that perhaps is evolving in maybe less
16 aggressive or less restrictions on those aggressive
17 interventions.
18 So it's an area of uncertainty. So it
19 requires perhaps again special attention in terms
20 of monitoring and trying to assess whether these
21 low levels might be harmful.
22 The point was made that the levels

1 themselves may not be being measured accurately
2 because as levels become very low, the methodology
3 is not as reliable. There is a tendency probably
4 for that to underestimate what the levels are. So
5 in other words, a very low level might not be quite
6 so low. And it's a little bit reassuring, but it
7 also was ultimately a little vague in terms of what
8 that might convey.
9 So the bottom line is that there is not
10 particular concern, but that's not to say it's not
11 a very, very important question, and there's really
12 a need for a lot more data to understand this.
13 Any additions, edits? Yes, Dr. Sager?
14 DR. SAGER: I would just add that the other
15 piece of information we don't know is if there's
16 really added benefit of going to extremely low
17 levels.
18 DR. SMITH: I think that's fair, and again,
19 that point was made that indeed important the
20 question is whether or not they may be benefit, and
21 that would help us, and there be maybe a lack of
22 benefit, and that would be help in another way in

1 terms of directing how to use an agent like this
2 that can achieve this response.
3 Anything else?
4 (No response.)
5 DR. SMITH: I think we'll go to discussion
6 question 2, and again, I'll read it. The applicant
7 has proposed two dosage regimens which were
8 selected to appeal to patient preference
9 considerations related to the dosing procedure and
10 frequency rather than to provide doses intended to
11 allow titration with respect to the magnitude of
12 LDL-C lowering.
13 Healthcare providers who are uncomfortable
14 with very low levels of LDL-C would either have to
15 down titrate other lipid-altering drugs, for
16 example, statin, or discontinue evolocumab.
17 Discuss whether you would have any concerns
18 with evolocumab not being labeled with dosage
19 regimens that provide varying degrees of LDL-C
20 lowering if approved.
21 Dr. Thomas?
22 DR. THOMAS: So I think the issue really is

1 what's the strategy if you are concerned by the low
2 LDLs and what's the advice or guidance. The
3 incorrect position probably would be based on data
4 we have, that is to reduce the statin. So there
5 needs to be some clear guidance or even in the
6 label of what to do.
7 I was actually very reassured by one of the
8 things that the sponsor actually mentioned an
9 alternative, which is using Zetia, that they didn't
10 feel that they have to be the first-line drug. But
11 they still need some guidance for practicing
12 physicians in terms of what to do.
13 The one thing that isn't problematic is it
14 really isn't a dosing regimen, at least from the
15 data we see, that allows you to really titrate up
16 or down while maintaining a smooth level because
17 there's going to be peaks and troughs. And that's
18 what I thought when the initial data was shown this
19 morning, and it really was confirmed by the
20 discussion.
21 But I think you have the strategy of not
22 lowering your statins and potentially lowering

1 other medications that lower cholesterol that might
2 be used in combination or a strategy of if your LDL
3 is too low and you're uncomfortable with that, both
4 patient and provider, you may use another agent
5 like Zetia, which has now documented efficacy in
6 some of these high risk populations.
7 DR. SMITH: Dr. Hiatt.
8 DR. HIATT: This question dovetails with 1C.
9 So I do have a concern because today if we make a
10 recommendation to approve, then we have uncertain
11 benefit, i.e., we don't have any clinical evidence
12 that the drug is effective until the outcome trial
13 is done. And I think we're faced with the real
14 possibility that physicians who focus on numbers
15 are going to look at very low levels and get
16 frightened whether that's for the right reason or
17 the wrong reason. And then they're going to back
18 off on the statin because they're not going to feel
19 as comfortable on a fixed dose prefilled syringe to
20 sort of fiddle with that because there will be a
21 sort of uncertain way to address that.
22 So I'm actually rather concerned about this.

1 I think that the interpretation of this question
2 may change when the outcome trial data are
3 released. If it turns out that, in fact, you can
4 stay on a fixed dose, go to extremely low levels on
5 some patients and have retained benefit or better
6 benefit with no additional risk concern, and you
7 can convince physicians not to back off on statins,
8 then it's probably not a concern.
9 But between now and then, I think it could
10 be a real concern, and it would be nice to have
11 those options. But I don't see exactly how you're
12 going to come up with those options in the next two
13 years because it's going to require the PK/PD kind
14 of relationships that it just takes some time to
15 acquire.
16 So the real problem here, I think, is that
17 if approved, physicians are likely to stay on a
18 dose of evolocumab that's going to be fixed and
19 back off on a statin that works definitively
20 without knowing how the combination is actually
21 working together until we have more data.
22 DR. SMITH: Dr. Rosenberg.

1 DR. ROSENBERG: Maybe I'm not as concerned
2 as some of the others. It may contribute to
3 changing the physician's mentality and follow the
4 guidelines that we need to treat not really
5 according to the LDL goal, but give the maximal
6 possible treatment that is appropriate given the
7 patient risk and circumstances, and leave it at
8 that.
9 That's really -- there's no really -- if you
10 follow those guidelines, no really reason to back
11 off on statin or anything else. Monitor for
12 security, for safety if you're concerned about a
13 very low level, but I think it will be a positive
14 development.
15 DR. SMITH: Dr. Shamburek.
16 DR. SHAMBUREK: I would concur with concern
17 Dr. Hiatt has and several others with -- I'm not
18 sure nowadays we can really rely on guidelines
19 because a lot of the new guidelines want evidence
20 based, and I'm not sure any guideline right now
21 will recommend Zetia in the absence of the
22 indication for IMPROVE-IT. So you're going to

1 still have to rely upon physicians who are very
2 indecisive now, and it's going to leave them in
3 limbo doing what they want.
4 But in the absence of a titrating drug, I'm
5 not sure of a good alternative. And perhaps until
6 you have an outcome, the better thing would be to
7 stop the PCSK9 inhibitor rather than titrating a
8 statin.
9 DR. SMITH: Dr. Sager.
10 DR. SAGER: I think that as a sponsor has
11 acknowledged, this could be handled through
12 labeling, that patients who -- you would not want
13 to decrease or stop the statin. And if that meant
14 having to stop this medication, then so be it if
15 one was really concerned that the LDL-C was too
16 low.
17 But I think it's really important until
18 there is outcome data, that hopefully will be
19 positive, that statin dosing be highly encouraged
20 and not in any way be cut back through the use of
21 other medications.
22 DR. SMITH: Dr. Blaha.

1 DR. BLAHA: Thank you.

2 I think this gets at the critical point of
3 who is going to get the drug, of course. At least
4 for the patients who I envision getting this drug
5 which, of course, include patients with FH who have
6 very high LDL cholesterols or patients who have
7 residually high cholesterol on a maximally
8 tolerated statin, I don't think we'll be seeing as
9 much of the critically low or very, very low LDL
10 cholesterol.

11 So for the indications for which I am
12 envisioning, I think I'm a little less concerned
13 about the inability to titrate. To me, it gets
14 back to the critically important question of who is
15 going to get the drug, and I think that's a
16 critical part of the discussion. I guess that's
17 the only point I'll make.

18 So I have less concerns about titratability
19 in the patients who I think are the most likely to
20 benefit.

21 DR. SMITH: Dr. Orza.

22 DR. ORZA: I think it's nice that we

1 actually have some information about and
2 consideration given to patient preferences. I
3 think that's the upside of this, especially as it
4 relates to improving adherence.
5 So the concern that I would have would be if
6 clinicians turn to the third option that's not
7 mentioned here, which is experimenting with off
8 label dosing strategies, that we then wouldn't know
9 the implications of that for adherence.
10 DR. SMITH: Dr. Wilson.
11 DR. WILSON: So just as a reminder, we
12 typically titrate patients to the maximum dose of a
13 statin, and then if we add another medicine, many
14 physicians simply add the other medicine. But many
15 physicians in lipid clinics back off from the dose
16 of a statin as they add the second medication.
17 So this becomes rather important down the
18 line because the maximum dose of statins is
19 historically associated with greater muscle
20 complaints and myalgias down the line, and it's
21 something I don't think you can make a
22 recommendation until you can get the data. But be

1 wary of the maximum dose of statins plus adding the
2 new medication.
3 DR. SMITH: Could I ask you to clarify that?
4 I'm still a little confused by what you mean by be
5 wary or --
6 DR. WILSON: Well, the concept is as you go
7 up for each dose of statin for most but not all
8 statins, the risk of myalgias, liver function, test
9 abnormalities and CK abnormalities goes up. Some
10 of them are relatively flat, but some of them go
11 up, and especially at the highest dose of the
12 statin prescribed.
13 Most of the patients here, for instance, you
14 would be talking about atorva 80 and rosuva 40.
15 Atorva 80 is different from atorva 40. If you get
16 to 80 before you add the newer medication, it may
17 affect the myalgia reported risk and the side
18 effect profile.
19 These are in product inserts already. If
20 you carefully read many of the inserts, they
21 describe this. Not as many physicians are quite as
22 sensitive to the issue of the dose of statin before

1 they add a second drug.
2 DR. SMITH: Pardon me. I guess what I'm
3 trying to understand is whether your issue is that
4 the achieved maximum dose of statin may be less
5 because there's less of a motivation to achieve
6 that with an alternative drug, and thus it will be
7 lower, or whether your concern is that the
8 achievable level may be less because of some
9 pharmacological phenomenon, or something else.
10 I'm sorry.
11 DR. WILSON: It's simply that the highest
12 dose of a statin is associated with the greatest
13 complaints, and that's why that dose typically has
14 been the maximum dose used because the complaints
15 really accelerate at the highest dose.
16 DR. SMITH: Okay. So other comments?
17 (No response.)
18 DR. SMITH: I'll summarize, and if I don't
19 address that properly, you can come back in with
20 it.
21 So again, the concerns being about -- or if
22 there are concerns -- the drug not being labeled

1 with dosage regimens that provide varying levels of
2 LDL cholesterol lowering and if approved.
3 In regard to this point, it does, in fact,
4 present concerns for some of the panelists. And
5 there is the concern that in use, if levels in
6 particular circumstances where the LDL-C levels may
7 become particularly low, that one might anticipate
8 that users will respond to that by making changes
9 in other medications and that that might in
10 particular include statins.
11 The focus has been on statins because it's a
12 group of drugs that really has the strongest data
13 and rather compelling data in terms of favorable
14 effects on cardiovascular outcomes. So an
15 intervention that lowered statin levels -- resulted
16 in a lowering of statin dose levels -- would be a
17 concern unless one had confidence that that was
18 being offset by the benefit of the alternative drug
19 being provided.
20 In that regard, the point was made that as
21 more outcome data become available from ongoing
22 study with evolocumab, that that might be helpful

1 in terms of addressing that situation.
2 The point was also made that as an option to
3 lowering the dose or to in this case not
4 administering evolocumab, there's a little
5 reassurance in how physicians might actually use
6 the drug because there may be alternative drugs
7 such as Zeta available, which could be substituted
8 rather than just lowering levels of statins.
9 So would anybody else like to make any
10 additions or modifications on that?
11 (No response.)
12 DR. SMITH: So let's go to the next
13 discussion question. This is question 3. For
14 homozygous familial hypercholesterolemia, HoFH, the
15 applicant has proposed a recommended dose of
16 evolocumab of either 420 milligrams once monthly or
17 420 milligrams every 2 weeks. Discuss whether the
18 applicant has provided adequate data to
19 characterize the efficacy and safety of the
20 420-milligram Q2W, every 2-week dosage, in this
21 population. And so we'll start with Dr. Nason.
22 DR. NASON: Thanks. I just wanted to jump

1 in on this because I don't necessarily think that
2 the 420 Q2W dose has really shown efficacy as
3 compared to the 420 monthly. I think -- I don't
4 have any real reason to believe there's a safety
5 concern other than there's not much data there.
6 There's not many people, and the people who were
7 given the Q2W instead of it really just
8 being -- well, it seems that they were -- it was
9 mostly based on the severity of their disease, so
10 it's hard to make any sort of comparisons there as
11 far as the efficacy.
12 When people were up titrated from the
13 monthly to the every 2 weeks, that change -- to me,
14 I'd need to see more data and more evidence that
15 that's a real change and not just within the
16 variability from time point to time point, because
17 it looked to me like at 4 weeks, they'd been a
18 little lower; at 12 weeks, they were a little
19 higher. And then when they went
20 down -- sorry -- when they increased their dose,
21 they were maybe back to where they were before at
22 the 4 week.

1 So I just would want to see more data before
2 believing in the efficacy. As far as safety, I
3 have no reason to think it's not safe, but no real
4 reason to think it is safe as far as the small
5 numbers of people.
6 DR. SMITH: Dr. Thomas.
7 DR. THOMAS: I agree with Dr. Nason. The
8 same issue is if you prespecify the initial point
9 where the LDL cholesterol was lower and then
10 measured it at 12 weeks, you probably wouldn't see
11 a difference, or very minimal difference, that may
12 not justify an additional dose.
13 If the trial had been carried out to a
14 longer period, we could at least assess if it's a
15 sustainable reduction or even a greater reduction
16 over, let's say, 24 weeks. So I don't feel that
17 actually there's sufficient evidence at this point
18 to support the other dosing regimen.
19 DR. SMITH: Dr. Burman.
20 DR. BURMAN: Thank you.
21 I agree with the comments that have been
22 made. But the change in LDL concentration was

1 approximately 6 percent with a higher dose, but
2 that was inconsistent. That is somewhat of a
3 concern. However, a 6 percent change in this
4 population theoretically may have cardiovascular
5 benefits, but that certainly isn't proven at the
6 moment.
7 The safety seems relatively well proven,
8 shown to be safe, with some minor hints of
9 potential minor problems. And if it's approved, I
10 think for the 420 milligram dose every 2 weeks, it
11 has to be emphasized that that is only for this
12 group of patients and should not be used for other
13 patients because it hasn't been studied in those
14 groups.
15 DR. SMITH: So would you support that dose
16 or not?
17 DR. BURMAN: That's a good question.
18 (Laughter.)
19 DR. BURMAN: I'm tending to support it
20 because of the group of patients that are being
21 evaluated with this severe homozygous familial
22 disease.

1 DR. SMITH: I'm sorry to turn that into a
2 voting question for you. That wasn't really fair.
3 DR. BURMAN: No problem.
4 DR. SMITH: Dr. Shamburek.
5 DR. SHAMBUREK: Yes, I think there is a very
6 important unmet need here in the homozygous FH, and
7 23 percent mean change in the non-apheresis
8 homozygous FH patient is going to be very
9 important.
10 I would concur with our others that I'm not
11 convinced the 420 milligrams Q monthly switched to
12 every 2 weeks. The 6 percent, which is
13 25 milligrams, although it is a difference, I'm not
14 sure we have enough information that it would
15 warrant it.
16 The one thing I do hope is that the approval
17 of this will not lead to discontinuation or prevent
18 patients with from going LDL apheresis, which seems
19 to be very helpful in itself and probably
20 complementary to receiving the PCSK9 inhibitor even
21 though it's a major inconvenience.
22 I also strongly think that the adolescent is

1 an important target group, and I really believe
2 that the early treatment will be helpful. And once
3 we have outcome trial on that, I even hope it will
4 go in younger homozygous FH children.
5 DR. SMITH: Dr. Blaha.
6 DR. BLAHA: I'll echo what others have said.
7 Certainly, this specific population would be the
8 only instance where I'd think we'd have any
9 evidence of safety and efficacy. But in those
10 patients, those select rare patients with severe
11 homozygous familial hypercholesterolemia, I think
12 the chance of even a small increase in the
13 reduction of LDL cholesterol could be very
14 beneficial.
15 So I think in this specific population, I
16 think it's reasonable to consider the 420 Q 2-week
17 dosing.
18 DR. SMITH: Dr. Budnitz.
19 CAPT BUDNITZ: I was just going to add to
20 the comments of the folks. I was a little
21 counterintuitive. I didn't quite understand the
22 sponsor adding this marginal difference for a

1 different dosing for this one subgroup but not
2 considering in the previous question a lower dose
3 for the other subgroups that could be titrated. I
4 didn't quite understand that logic.
5 DR. SMITH: So I will try to summarize. The
6 view was expressed by more than one panel member
7 that the data really do not provide convincing
8 evidence that there is a meaningful difference in
9 the higher dose versus the lower dose. And to
10 resolve that question would simply require more
11 data. There's no adequate data to do that.
12 The point was also made that even though the
13 difference between those two doses is small and the
14 reality or validity of that difference remains
15 uncertain, that we're addressing a group of
16 patients with a particularly clinically severe
17 disorder in which even a modest further lowering of
18 LDL-C might be beneficial. And given that
19 situation, panel members, at least a couple panel
20 members, also expressed the view that until more
21 information is available, they would favor using
22 the higher dose.

1 In part, that position is driven by an
2 absence of safety signals of concern, again
3 recognizing that there's a very small data pool
4 from which those safety signals are derived, but
5 there are not alarm signals there.
6 So that I'm expanding a little here, but
7 supporting the use of a higher dose, it's important
8 to recognize that's in a context of current low
9 level of concern with safety signal, and that could
10 change if more information came out about safety.
11 The point was also made that one would like
12 to see strong consideration given in use in
13 particular, or consideration also, maybe in the
14 younger population of affected patients where there
15 might be particular opportunity for benefit as
16 well.
17 Anything anyone would like to add or amend
18 from that?
19 Okay. So -- yes, Dr. Thomas.
20 DR. THOMAS: I may just have misheard it,
21 but I would actually I think we feel that the
22 6 percent change is meaningful, but some of us are

1 not sure that the 6 percent change is real. So I'm
2 not sure that we would advocate for the higher
3 dose.
4 DR. SMITH: I understand. So we might just
5 amend that summary that some panel members have
6 expressed support for the notion of a higher dose
7 until one knows otherwise because perhaps there's a
8 lower level of LDL, and other panel members
9 expressed the concern that actually we don't know
10 whether it's lower or not because of the limited
11 amount of data. So it's not an easy answer and not
12 a clear answer.
13 So what I would like to do now is take a
14 15-minute break. I would ask you, as I have
15 before, that panelists should not during the break
16 discuss any of the issues that are before the panel
17 today among themselves or with any other members of
18 the audience. And we'll be back here at 3:30,
19 where we'll resume with the next part of this
20 discussion and voting.
21 (Whereupon, at 3:13 p.m., a recess was
22 taken.)

1 DR. SMITH: So welcome back. I think we'll
2 take up with now discussion question 4. Again,
3 I'll read this question.
4 The goal of LDL-C lowering therapy is to
5 reduce the risk of cardiovascular disease.
6 Historically, a change in LDL-C has been considered
7 sufficient to establish the effectiveness of a
8 lipid-altering drug intended for use to reduce
9 cardiovascular risk without any regulatory
10 requirement to demonstrate evidence for benefit in
11 a cardiovascular outcomes trial provided the
12 reduction is sufficiently robust and the product or
13 its class does not have safety issues that raise
14 concern that risk exceeds benefit.
15 Discuss whether evolocumab-induced LDL-C
16 lowering is sufficient to substitute for
17 demonstrating its effect on clinical outcomes,
18 i.e., to substitute for investigation in a CV
19 outcomes trial in one or more populations, for
20 example, different degrees of cardiovascular risk,
21 familial versus non-familial etiologies of
22 hyperlipidemia, use with or without concomitant

1 statins, et cetera."
2 So this is open for discussion.
3 (No response.)
4 DR. SMITH: Oh, come now.
5 (Laughter.)
6 DR. SMITH: Dr. Thomas.
7 DR. THOMAS: So since I wasn't struck by
8 lightning since yesterday, I won't change my
9 opinion.
10 (Laughter.)
11 DR. THOMAS: But actually LDL cholesterol is
12 probably one of the more robust surrogates that we
13 have. Many trials have supported eventually,
14 though, that if you lower LDL cholesterol, that you
15 do have decreased events and primarily statins.
16 I think where we run into issues are that in
17 the area of statins, most of these trials are
18 add-ons, and the amount of LDL cholesterol is much
19 lower than initially. So I don't think that the
20 premise of LDL lowering has changed, and I still
21 think it's a reasonable surrogate for approval,
22 assuming all the other safety risks are addressed.

1 Some of the examples that were brought up
2 like torcetrapib, there's a safety signal. So even
3 though it did lower cholesterol, the safety signal,
4 which was off target, is really the issue, not that
5 the LDL cholesterol is an inappropriate target to
6 use for efficacy.
7 DR. THOMAS: Dr. Hiatt.
8 DR. HIATT: This is a question I struggled
9 with mightily the last two days, and I think that
10 the way the FDA's framed this both yesterday and
11 today is obviously consistent. It asks us whether
12 we have enough confidence in LDL as a surrogate
13 across all drug classes to make a decision about a
14 drug that has minimal -- has little safety data and
15 no outcome data based entirely on a surrogate
16 endpoint.
17 Now, of course, I recognize that the
18 mechanism is highly similar to statins, that
19 statins have conclusive evidence, that an outcome
20 trial has been enrolled and will be fully informed
21 in the very near future.
22 But if we took this approach, and the first

1 new molecular entity that we were now discussing
2 today was niacin, even though its effects were
3 modest, we would say we would approve that drug
4 because it lowered LDL cholesterol. And we would
5 then have found out with outcome trial data later
6 that it really doesn't reduce clinical events.
7 So I'm of the position today that it would
8 be important to have clinical evidence of benefit
9 for a new molecular entity before making a
10 decision, and that a surrogate is insufficient to
11 do that, and that the necessary information around
12 risk and benefit has not been established with the
13 development program to date. And therefore, I
14 would feel that the results of a cardiovascular
15 outcomes trial be necessary to make an informed
16 decision.
17 DR. SMITH: Dr. Shamburek.
18 DR. SHAMBUREK: I think we heard a lot of
19 compelling data this morning showing the
20 correlations between LDL and cardiovascular
21 outcome, and I do believe LDL and other
22 lipoproteins are biomarkers. But I also do believe

1 that LDL in certain circumstances is a surrogate
2 for cardiovascular risk. And we rely on surrogates
3 when we often don't have cardiovascular outcomes or
4 we rely on them when they're proven, such as with
5 the statins.
6 I think 10 years ago with LDL and sometimes
7 the LDL hypothesis, we felt more reassured, and I
8 think in the last 10 years, there have been several
9 trials. There's been the torcetrapib CETP
10 inhibitor, the estrogen, fibrates. Some of those
11 have come up. And one of the reasons described
12 this morning was the modest effect of LDL, and I
13 think that's certainly is one. But I think more
14 compelling is the mechanism in which it works.
15 I think LDL becomes a surrogate in studies
16 such as the statins where they're affecting LDL
17 receptors, and I think that same mechanism is going
18 on with the PCSK9 inhibitors. And I think even
19 stronger to that support is the fact of what we
20 know about PCSK9 when we have genetic defects or
21 FH, things like that.
22 So I think when I feel more compelled to

1 call it a surrogate in this era when there are
2 modulations of LDL, but in those studies you see
3 changes in triglyceride and HDL. And the effect on
4 LDL in my mind in those studies is a secondary one.
5 When the primary effect is one the LDL receptor, I
6 feel that's when LDL becomes more of a surrogate.
7 DR. SMITH: Dr. Burman.
8 DR. BURMAN: Thank you. I agree with the
9 comments made. Dr. Smith in his nice discussion
10 said that to be used as a surrogate, it has to be
11 quote, unquote "substitute" for a clinically
12 meaning endpoint, et cetera. So if I use that
13 strict definition, I think LDL is not meeting that
14 because I don't know that it's a substitute in this
15 circumstance, but I think it's highly likely or
16 highly probable that it will be a surrogate in the
17 future.
18 DR. SMITH: Dr. Orza.
19 DR. ORZA: I wasn't struck by lightning
20 either, and so I am pretty much in the same place I
21 was yesterday in thinking that we should no longer
22 settle for the surrogate endpoint, but we should

1 make the standard outcomes data.
2 But what we discussed briefly yesterday
3 about maybe for certain populations, in this case,
4 I'm thinking of the HoFH population, that it's not
5 really a surrogate so much as an endpoint in and of
6 itself, that there is something about lowering the
7 LDL cholesterol of people who have these extremely
8 high levels, especially if there are actually
9 physical manifestations of that, which we didn't
10 talk about yesterday.
11 I'm going to mispronounce what they are, but
12 if lowering their LDL cholesterol actually helps
13 with those -- what were they called?
14 DR. SMITH: Xanthomas.
15 DR. ORZA: That makes it less of a surrogate
16 and more of an actual endpoint.
17 DR. SMITH: Dr. Budnitz.
18 CAPT BUDNITZ: Similar to yesterday and
19 making a similar point first that I do have
20 concerns about using LDL as a surrogate endpoint
21 for all drug classes. But in the context of
22 disease like familial hypercholesterolemia, maybe

1 it's a little mental gymnastics, but I don't think
2 LDL is a surrogate endpoint in that case. Similar
3 to the disease of PKU, phenylalanine, it's a direct
4 effect of a problem of metabolism that's a pinpoint
5 genetic defect.
6 Just like we wouldn't wait for a outcomes
7 study to demonstrate improvement in brain damage if
8 we could do something to improve phenylalanine
9 metabolism for PKU patients, I don't know if we
10 need to do the same kind of outcomes work for
11 something where the mechanism is so potentially
12 clear.
13 Now, I know that there are heterozygous
14 patients and different mutations, but at least if
15 it can be documented with the genetic testing that
16 we have available, I think that in this context,
17 LDL may not be a surrogate endpoint, and we could
18 assess the product in that way.
19 DR. SMITH: Dr. Nason.
20 DR. NASON: I agree with much of everything
21 that's been said, including the need for
22 cardiovascular outcomes as we move into a new drug

1 class, especially given that that was mostly based
2 on statins and also with the exceptions in the FH
3 patients.
4 One thing I just wanted to add, and maybe
5 it's just a plea for whoever is going to write the
6 next sort of definitive paper trying to look at
7 whether this is a surrogate. Meta-analysis are
8 very useful, and seeing the trials on that line is
9 very useful. But it's not the same as seeing
10 individual level data or very small subgroups of
11 data because you can end up with paradoxes where
12 things look sort of correlated on a drug by drug
13 level, but they don't necessarily have the same
14 structure when you look on an individual level.
15 So I would -- not right now, I'm not asking
16 you guys to scramble. I'm just saying that I think
17 moving forward with this question, I think it will
18 be useful to think about that across classes,
19 across statins and non-statins on more of an
20 individual level, looking at the relationships
21 between LDLs and outcomes as much as possible to
22 try to answer that question, and possibly modeling

1 for other known predictors and other known effects.
2 DR. SMITH: Dr. Sager.
3 DR. SAGER: Given the lack of some trials,
4 which show an LDL-C reduction but didn't show
5 decreases in cardiovascular morbidity and
6 mortality, then I think we can't be sure. And we
7 don't want to overreach until we actually have the
8 outcome trial data.
9 However, based on the mechanism of action,
10 the genetic data, the likelihood that these very
11 large LDL-C reductions -- and importantly, without
12 evidence of any strong safety signal -- will
13 actually translate into reductions in
14 cardiovascular events, I personally think is
15 relatively likely. And the patient populations,
16 clearly that will benefit the most are those who
17 are really at high risk, those with FH and very
18 high cardiovascular risk.
19 DR. SMITH: Dr. Rosenberg.
20 DR. ROSENBERG: I wasn't there yesterday, so
21 I cannot agree or contradict myself.
22 (Laughter.)

1 DR. ROSENBERG: I won't elaborate a lot more
2 about the issue about surrogates, just to say that
3 I don't think there's much doubt that any large
4 reduction in LDL is related to a decrease in
5 cardiovascular risk, provided you don't have any
6 off-target effect.
7 I would like to say that in the lack of
8 clinical data that are pending, we probably need to
9 consider which population we're targeting. And for
10 any new drug, usually when you're testing its
11 effect, you want to test it in the population at
12 high risk where the benefit is most likely to
13 exceed the risk.
14 So if this drug is to be considered while
15 clinical outcomes are pending, you probably want to
16 focus on the highest risk population where you
17 think this risk/benefit ratio is going to be
18 beneficial or benefit/risk.
19 DR. SMITH: Dr. Blaha.
20 DR. BLAHA: So likewise, I have similar
21 comments from yesterday, but I'll reiterate those.
22 I do think that the candidacy of LDL-C as a

1 surrogate is population and mechanism dependent.
2 Certainly, FH and, let's say, someone with elevated
3 lipids in primary prevention are certainly
4 different cases. FH is a genetic disorder, exposed
5 to lifelong levels of LDL lipoproteins that is
6 clearly the primary cause of one's atherosclerosis.
7 And targeting that in a selective way, especially
8 with an antibody, has great appeal. However, using
9 LDL-C as a surrogate in the larger primary
10 prevention, to me, is a different question.
11 I also think it's mechanism dependent, as
12 we've talked about over the last two days. The
13 biology, the genetic data, all point to PCSK9
14 inhibition being potentially a favorable mechanism
15 of attacking elevated lipoprotein load.
16 Now, I'll remind everyone of course,
17 likewise, the Mendelian randomization data for CETP
18 has not been reassuring. So we're probably talking
19 about more than just the LDL-C hypothesis. We're
20 talking about the LDL or maybe ApoB or lipoprotein
21 load hypothesis, where if you're getting all your
22 lipoprotein data going in the right direction such

1 as LDL-C lowering but also ApoB lowering, allele
2 particle lowering, we're probably talking about a
3 good surrogate. There's probably instances where
4 LDL-C doesn't tell us everything we need to know
5 about the lipoproteins. But in this case with the
6 genetics and biology lining up, I think LDL-C is a
7 reasonable surrogate, especially for patients who
8 have FH.
9 DR. SMITH: Dr. Wilson.
10 DR. WILSON: So the term that I first read
11 about yesterday, and it's in today's handout, is
12 coined I think by Dr. James Smith for the FDA. And
13 I think the term. It's LDL-C is "context
14 dependent" which means it depends.
15 It depends on where we are in the gradient
16 for LDL and CVD risk. And as we get lower, most of
17 us feel that this risk is flattening out because
18 it's more of a S-shaped curve and not simply a
19 straight line going right through zero or through
20 the Y-axis, and we wrestle with that.
21 Will Hiatt, I think, has said it best, and
22 the speakers from the public forum had an elegant

1 slide, actually summarized what Dr. Hiatt has said
2 yesterday and some of what he just repeated.
3 So it's context dependent, and we really
4 should be careful with newer medications and at
5 lower LDL cholesterol levels.
6 To end on this, we have an analogy for this
7 a little bit with blood pressure and with glucose.
8 You can't keep driving everything down, as we've
9 seen in major trials. We need to know, as just
10 mentioned, the benefits and the concerns. So we
11 need to do the studies, especially at the lower
12 levels.
13 This is definitely a context-dependent
14 question, and where we are in the LDL curve at the
15 starting point effects how we answer.
16 DR. SMITH: So I'll endeavor to summarize.
17 In asking this question, the FDA in a sense
18 targeted their question in terms of discussing
19 whether evolocumab-induced LDL-C lowering is
20 sufficient. And the panel members embraced that
21 and went further in terms of answering this
22 question in a context-specific manner, making the

1 point that this is not a question that is the
2 suitability of LDL-C as a surrogate, a substitute.
3 This is not a question that can be readily answered
4 broadly for all agents that might affect LDL-C, and
5 that even within this specific drug treatment with
6 evolocumab-treated subjects, again, it's important
7 to consider this in a context-dependent manner.
8 So in regard to the drug itself, the point
9 was made that it targets LDL-C in a mechanism
10 that's fairly close to the targeting that statins
11 do. And given the statin database, that's
12 encouraging in strengthening someone's confidence
13 in this as a surrogate.
14 The point was also made that for certain
15 population groups such as those with familial
16 hypercholesterolemia, that at least for many of the
17 patients we classify in that group, there's such a
18 compelling mechanistic link to LDL-C as a
19 pathogenic factor, that again, that strengthens
20 one's confidence in this as an adequate surrogate.
21 The point was raised that beyond that, it's
22 important to recognize that the starting point for

1 the LDL level as it is lowered may be important to
2 consider because there may be an S-shaped curve,
3 and there's evidence for that, such that lowering
4 higher levels may have a different benefit in terms
5 of outcomes than lowering lower levels, and there's
6 a need for more data to bear on that.
7 That sort of leads into a very important
8 point that was expressed by the panel members,
9 which is that while endorsing the concept that
10 LDL-C is a pretty good surrogate in the context
11 that I've just described with this drug, that that
12 does not in any way offset the need for ultimately
13 cardiovascular outcome trials; and that is that
14 there remains very important questions about the
15 ultimate efficacy and benefit from this agent that
16 can only be answered by carefully designed and
17 conducted CVOT. So it's really part of the package
18 as well.
19 Would anybody like to add anything to that?
20 (No response.)
21 DR. SMITH: Okay. So I think we move to the
22 first of the voting questions. Questions 5 and 6

1 are both voting questions, and we're going to be
2 using an electronic voting system. Once we begin
3 the vote, the buttons on your microphone will start
4 flashing, and they'll continue to flash even after
5 you've entered your vote. You're asked to please
6 press the button in accordance with the vote that
7 you want to make firmly. If you're unsure of your
8 vote or you wish to change your vote, you may press
9 the corresponding button until the vote is closed,
10 that is, until it stops flashing.
11 After everyone has completed their vote, the
12 vote will be locked in. The vote will then be
13 displayed on the screen. The DFO will read the
14 vote from the screen into the record, and then
15 we'll go around the room and each individual who
16 voted will state their name and their vote into the
17 record. And then you have opportunity as you wish
18 to make comments about the rationale behind your
19 vote.
20 There's options for these questions of a yes
21 and a no and an abstain, and I would encourage you
22 to try to vote yes or no and not abstain, even if

1 you're finding it a difficult vote, because that
2 will perhaps be more helpful and then you have
3 ample opportunity to explain the challenges you
4 faced in choosing yes or no if that was the case.
5 So we can go to question 5, which is the
6 first voting question.
7 Yes, Dr. Smith.
8 DR. J. SMITH: I just wanted to reemphasize,
9 I know it's been a long couple of days for many of
10 you, and we're approaching the end. So I just want
11 to reemphasize how important it is to include your
12 comments, even if you felt like you've said a lot
13 of things repetitively here, for the vote and in
14 your comments following the vote when we go around
15 the table. Please address the patient populations
16 for whom you feel the benefit/risk is favorable if
17 you vote yes. Thanks.
18 DR. SMITH: So question 5, has the applicant
19 sufficiently established that the LDL-C lowering
20 benefit of evolocumab exceeds its risk to support
21 approval in one or more patient populations,
22 excluding HoFH, which will come up in the next

1 question. We remind you that under the current
2 regulatory pathway, it would not be required to
3 successfully demonstrate an effect of evolocumab on
4 CV outcomes after an approval based on changes in
5 LDL-C.
6 If yes, please explain your rationale, and
7 describe the patient population or populations for
8 whom you believe the benefit/risk is favorable. If
9 no, please describe what further studies you
10 believe the applicant must conduct to establish a
11 favorable benefit/risk to support approval.
12 Any questions in regard to the wording?
13 Yes, Dr. Blaha.
14 DR. BLAHA: I have a question. So I don't
15 think, if I heard right, that this was studied
16 specifically in a heterozygous FH population. And
17 question 5 refers to excluding homozygous FH. What
18 are we to make of heterozygous FH patients in the
19 interpretation of that question?
20 DR. SMITH: My interpretation is that
21 heterozygous FH is included in this question and
22 might be one of those sub-categories that you would

1 comment on if you were in a situation where you
2 wanted to do that. And it's only homozygous FH,
3 which is being addressed in the following question.
4 And I'm getting nods --
5 DR. WASSERMAN: Excuse me, Dr. Smith. I do
6 want to make a comment just to correct Dr. Blaha,
7 and I apologize if I misheard it. But we have
8 studied 500 HeFH patients in the question you were
9 about to address. And then in addition, there's
10 the homozygous, which we'll discuss later. But I
11 just want to make sure that it's clear, we have
12 studied heterozygous FH.
13 DR. SMITH: I don't think there was -- I'm
14 not sure that was uncertainty about that.
15 DR. BLAHA: I don't mean to cause
16 uncertainty about that.
17 DR. SMITH: So no other questions about the
18 wording, so we'll proceed with the vote.
19 (Vote taken.)
20 DR. BAUTISTA: The vote is now closed.
21 We'll now read the vote into the record. There are
22 11 yeses, 4 noes, and zero abstentions.

1 DR. SMITH: So you might take a look and
2 make sure your vote registered the way you did it,
3 and we will start going around the room. And what
4 I ask you to do is to state into your microphone
5 for the record your name, your vote, and then
6 please make comments on the rationale for your
7 vote. And I think we'll start with Dr. Cooke this
8 time.
9 DR. COOKE: David Cooke, and I voted yes. I
10 think my reason is that, to start with, I agree
11 with many of the comments for the prior questions
12 that LDL-C is not going to be a surrogate for all
13 classes of medications, but it's going to be
14 context and mechanism specific.
15 So for this medication and in the
16 context-related way, I think the sponsor has
17 demonstrated appropriate benefit for LDL-lowering
18 in those highest risk individuals, so those with
19 the higher elevations of LDL-C as would be seen in
20 heterozygous FH patients or those with high LDL-C
21 levels in the context of high risk cardiovascular
22 disease.

1 I'm a little more uncertain about the
2 patients that -- well, I think patients that are at
3 lower risk, both only modest elevations of LDL-C
4 and lower cardiovascular risk, I think in those
5 patients, I would recommend seeing evidence of
6 cardiovascular benefit for approving those as an
7 indication.
8 I think the middle ground, moderate
9 elevations of LDL-C, moderate cardiovascular risk.
10 I'm a little bit on the fence because I am fairly
11 convinced by the mechanism of this medication, in
12 terms of both its similarity to statins with LDL
13 receptor up regulation as well as the genetics of
14 the alterations in PCSK9 levels in humans and the
15 correlation with cardiovascular risk there.
16 So there, I'm a little bit uncertain about
17 the need for the cardiovascular outcome trial
18 before approval for that indication.
19 DR. STANLEY: This is Charles Stanley. I
20 voted yes. I think I'm much more convinced that
21 the drug has benefits in patients with heterozygous
22 familial hypercholesterolemia, both by the

1 mechanism of action. And I'm less convinced that
2 we're certain about the benefits in the other
3 populations of mixed dyslipidemia. And I think in
4 those populations, as we're evolving our thinking
5 about LDL cholesterol as a marker, as a surrogate,
6 that the field is going to change and begin to
7 demand more cardiovascular outcome trials to
8 demonstrate benefit.
9 But I think for the heterozygous familial
10 hypercholesterolemia patients, I think it's fairly
11 convincing that the benefits outweigh the risks by
12 a great deal.
13 CAPT BUDNITZ: Dan Budnitz, I voted yes for
14 the indication of heterozygous familial
15 hypercholesterolemia. As I mentioned before, I see
16 the LDL in this context or group of patients really
17 less as a surrogate and more of an outcome
18 variable.
19 But I am very much, like others on the
20 committee, looking forward to the large outcomes
21 study that is underway to try to get additional
22 information on not just more patients, but more

1 patients over a longer time period with exposure to
2 this medication, both for outcomes as well as
3 adverse effects and would hopefully look forward to
4 if the outcomes are positive and adverse effects
5 are fully explored over longer-term exposure seeing
6 broadened indications for other patients.
7 One other point of concern for indications
8 regarding intolerance and folks at very high risk
9 for me is just how that is defined in the label and
10 in clinical practice. To extend a further
11 indication without the outcomes data in this
12 population I think is problematic, particularly
13 when hopefully there is outcomes data in a
14 relatively short time period.
15 DR. ORZA: Michele Orza. I voted again a
16 reluctant yes in order to be consistent with myself
17 and hopefully not foolishly so. I think that given
18 the lack of evidence about cardiovascular outcomes
19 on the one hand and the insufficient evidence on
20 the safety side, that the risk/benefit equation
21 really only balances out for the population that's
22 suffering from very high levels of cholesterol, is

1 at very high risk for poor cardiovascular outcomes,
2 and needs additional options in order to be able to
3 manage that. And I think that means the HeFH
4 population.
5 MS. MCCALL: Debra McCall. I voted yes
6 specifically for the HeFH population and those at
7 high cardiovascular risk.
8 As has already been mentioned, I am a
9 smidgen concerned about the short duration of the
10 study. I would have preferred longer. But I also
11 would like to give a real positive shout-out to the
12 sponsor for giving two dosing options to the
13 patients.
14 Those of us who take medications long-term,
15 medication fatigue, pill fatigue is a real thing.
16 So having the option to do it every 2 weeks or
17 monthly is a big plus, and it's thoughtful. I
18 think this opens the conversation for the patient
19 and prescribing physician to have a really good
20 discussion about what's best for this particular
21 patient.
22 Also speaking for the patients, for those

1 that came today and stood up in front of this
2 really big room and very scary people, well done.
3 I know how frightening and intimidating it can be.
4 And you really made a difference by coming today,
5 and that's why we're here.
6 DR. BURMAN: Ken Burman, I voted yes. I
7 think that evolocumab has been shown to be
8 effective in lowering LDL in the following groups:
9 non-familial hypercholesterolemia, high-risk
10 patients with elevated LDL levels on statin therapy
11 who have not reached goal LDL levels; high-risk
12 patients who can't take -- or who are intolerant to
13 statins and; of course, heterozygous familial
14 hypercholesterolemic patients.
15 Without further long-term studies and
16 analysis, I don't think the medication should
17 routinely be used as sole therapy in low-risk
18 patients with normal or mildly elevated LDL
19 concentrations.
20 My decision is try to balance opposing yet
21 equally valid views. On the one hand,
22 cardiovascular outcomes trials are extremely

1 important and it is not yet proven that they will
2 be successful. On the other hand, it will take at
3 least two or three years to establish
4 cardiovascular event results. And in the meantime,
5 I think the lowering of LDL is a reasonable
6 surrogate to continue to support this medication.
7 Thank you.
8 DR. THOMAS: Abraham Thomas. I voted no,
9 and there are a few reasons. First, really the
10 assessment of safety. Even though there was no
11 signal, the duration of the trials were too short
12 for me. At 12 weeks, it's a few doses, and some of
13 the effects that we're looking at require probably
14 a longer time, diabetes being one of them.
15 If you think about anti-psychotics, the rate
16 of conversion of a drug like olanzapine is about
17 7.5 percent over the course of a year. Over
18 12 weeks, it's really hard to assess what the
19 diabetes risk is, and that may carry over to other
20 safety signals.
21 So I felt very uncomfortable with such a
22 short duration for most of the trials and only

1 having one trial of sufficient duration that was
2 blinded and controlled to 52 weeks.
3 The second part of that is observational
4 studies or extension studies should be there to
5 support efficacy or safety but not acceptable as a
6 substitute for long enough trials with proper
7 randomization and blinding. And if there is some
8 question about the ethics of using such a trial
9 that's blinded, instead of a placebo comparator, an
10 active control comparator could be used. And there
11 are alternatives that could be used to design the
12 trials.
13 One of the things that is also a problem is
14 the population. The population that was studied in
15 the longer trial, many of those patients may not
16 even get therapy under our current indication. So
17 if we're going to look at safety, we should
18 probably look at it eventually in the people who
19 are going to be most likely to be treated. And I
20 didn't think there were sufficient number of
21 patients to really assess that in the 52-week
22 trial, which is the only one I'm really going to

1 use for the evaluation of safety based on the ones
2 that were presented. So there does need to be more
3 people who are going to be the ones that we treat.
4 Now, the good thing is part of this question
5 is what would we suggest to the sponsor, and I have
6 to say to their credit has a well thought out
7 outcomes trial. And it's such a large number of
8 subjects, they should be able to answer all of the
9 safety questions or at least most of them that
10 would be concerning.
11 The second thing I just also want to commend
12 them for their thoughtfulness in being proactive
13 and putting the energy, the time, and the resources
14 into doing a neurocognition study.
15 I appreciate that they're going to do that
16 instead of the hand waving I got yesterday about
17 what we're doing is fine. I actually really think
18 it's a credit to the sponsor that they're going
19 ahead with that already because that is an
20 important question, whether it's favorable or
21 negative or neutral.
22 Finally, I still voted no except for one

1 group, heterozygous FH patients really do, I think,
2 deserve to have this agent because they're a group
3 if they're not a target for LDL that they should
4 have some other options, and this is the first in
5 this class that could be approved. And I would not
6 delay it for that population based on the other
7 groups that may need further study or evaluation.
8 DR. BLAHA: Michael Blaha. I voted yes. In
9 particular, I voted a strong yes for patients with
10 well documented heterozygous FH, which have a
11 genetic lipid disorder, which I think is very
12 appropriate for use of this drug for lowering of
13 LDL-C as a valid surrogate for the expected
14 cardiovascular benefit in those patients.
15 I also would vote a yes for patients in
16 high-risk secondary prevention, not primary but
17 secondary prevention, and those are the less than
18 anticipated response to maximally tolerated statins
19 and who have residually high LDL or ApoB, which in
20 some cases will include some patients with very
21 well documented statin intolerance who couldn't
22 achieve a sufficient LDL lowering on maximally

1 tolerated or, in this case, not tolerated at all
2 statin.
3 Many of these patients, of course, who have
4 residually high LDL after maximally tolerated
5 statin, these patients have heterozygous FH that's
6 undiagnosed. So once again, it's another
7 endorsement for the use in heterozygous FH or in
8 patients who we think have heterozygous FH once
9 extrapolated back to their baseline LDL before
10 statin therapy.
11 I would vote no for patients who are
12 so-called statin intolerance broadly interpreted,
13 particularly those patients at primary prevention
14 with so-called statin intolerance, given the
15 difficulty in defining such a term.
16 Any circumstance that would lead to more use
17 of this medication as routine monotherapy before a
18 cardiovascular outcomes trial, I would not be in
19 support of that. Also, I'm not supportive of the
20 use of this medication for diabetic dyslipidemia or
21 other dyslipidemia, especially where lifestyle
22 could also be another therapeutic goal. Thank you.

1 DR. SMITH: I'm Robert Smith. I voted yes.
2 I mean that yes meaning approval in the current
3 context for a target population specifically of
4 individuals at high cardiovascular disease risk,
5 those we're describing as heterozygous familial
6 hypercholesterolemia, and other less well defined
7 patients perhaps who have high risk and have
8 associated with that high LDL cholesterols in spite
9 of treatment with statins and other available
10 agents.
11 I'm motivated to make that vote because I
12 think those individuals have an unmet need and they
13 have an urgent need for therapy. So I'm unwilling
14 to wait for the period of time until completion of
15 outcome trials before giving them that option.
16 That's not to say that I am totally
17 convinced that the LDL lowering we see will play
18 out into cardiovascular benefit. It's a
19 willingness, in my view, to accept that uncertainty
20 while we figure that out. And so it becomes
21 absolutely critical to complete adequate
22 cardiovascular outcome trials to answer the true

1 outcome benefit question.
2 I'm motivated in part in taking this
3 position by the fact that this is a new drug class
4 that then offers a new avenue of therapy in an area
5 where, as I said, there truly is unmet need with
6 currently available drugs and interventions.
7 I'm motivated in part by the strong effect
8 on LDL cholesterol, and so it's not a small
9 decrease which I'm uncertain about. It's a very
10 large decrease, and even though I have uncertainty,
11 I think there's an opportunity I don't want to
12 forego.
13 I'm motivated in part by the fact that I'm
14 not concerned about adverse safety issues based on
15 the data that we've seen. And again, the data are
16 not adequate to be fully reassuring that there
17 aren't safety problems, but there are not signals
18 that are alarming.
19 I recognize that there are mechanisms
20 postmarketing that I would anticipate would be
21 employed to be gathering further useful data and
22 hopefully would discover any safety problems were

1 they to occur.
2 I do think it's important, again, in terms
3 of carrying out what my position would be, would be
4 very important in terms of labeling and other ways
5 of communicating with users to endeavor to minimize
6 any effects of use of this drug on decreasing the
7 use of statins, which we have the strongest
8 evidence for their benefit. So there may be
9 negative consequences of use of this drug if we
10 were to reduce statin doses.
11 DR. HIATT: I'm William Hiatt, and I voted
12 no. I voted no for three reasons. The first
13 reason is that accelerated approval is not an
14 option, which I think is unfortunate. I'm not
15 challenging why that's not an option. But in this
16 situation, it would have allowed us to be assured
17 that a cardiovascular outcome trial would have to
18 be completed and that would have resolved my
19 concern.
20 But without that option, a yes vote means
21 that we're going to expose a large population of
22 patients to a drug that has a very limited safety

1 database and absolutely no clinical evidence of
2 benefit.
3 My second point is implications for future
4 drug development. A yes vote means we support LDL
5 as a surrogate under all conditions, and that
6 therefore increases the probably that new drugs
7 testing very novel mechanisms that don't work
8 through LDL receptors may get approved based on LDL
9 that perhaps could have lots of pleiotropic
10 effects, one of which may be LDL lowering.
11 But the drug could have other effects on
12 other lipid or other metabolic parameters that are
13 presumed to be favorable, but the sponsor could
14 simply pick LDL as the target and get approved for
15 that reason. And we would have -- I would have
16 more uncertainty if this mechanistic approach
17 didn't seem to make sense in terms of what we know
18 about what benefits patients in terms of LDL
19 lowering.
20 My third reason to vote no is that the
21 approach to approval for LDL is very different than
22 the approach for approval for clinical benefit.

1 That approach was adopted at diabetes drug
2 development where you can perform lots of little
3 trials, quickly modify A1c, and get a drug on the
4 market for all kinds of patient populations with
5 lots of different comparators.
6 The problem with that is we got in trouble
7 around cardiac safety, and that triggered a whole
8 bunch of safety trials to address the question that
9 a series of small limited studies targeting A1c
10 could not possibly answer.
11 Now we've got an efficacy issue, I think,
12 and if we continue to support LDL as the approval
13 surrogate, then through a series of small trials of
14 12 weeks or 24 weeks with a robust effect on LDL,
15 you can get on the market. And I think that that
16 is a risky precept to continue to follow today when
17 what we're really trying to do is understand
18 clinical benefit.
19 So I think there are three strong reasons to
20 vote no in this situation.
21 DR. WILSON: Peter Wilson. I voted no for
22 many of the same reasons very well expressed by

1 Will Hiatt. In addition, to go back to what
2 Abraham Thomas mentioned, I think we need longer
3 exposures to this new product, especially 26-,
4 52-week studies. I just can't come to conclusions
5 about some of the safety signals for some of the
6 subgroups with the shorter studies.
7 I'm particularly concerned if the agency
8 were to approve the drug, there'd be a large number
9 of people for whom there may be very little
10 benefit. And by my back of the envelope
11 calculations of a 2 percent difference in the
12 preliminary data that have been presented and some
13 of it's published up to now, that means if I take
14 50 patients on a statin and I give them this new
15 product, one of those 50 will benefit.
16 So I have 49 who don't benefit. That's not
17 the same sort of place where we are for initial
18 drugs. That's where we sort of are also for
19 ezetimibe. So these are tough decisions,
20 especially for people already on statins who may or
21 may not be obtaining benefit. I think we should
22 exercise caution, and we need those outcome trials.

1 DR. ROSENBERG: Yves Rosenberg. I voted yes
2 for many of the reasons that Dr. Smith and others
3 have expressed. I would have voted no if not for
4 the sponsor's clear commitment to long-term
5 follow--up studies, which some are ongoing, as well
6 as clearly specifying that this drug should only be
7 prescribed in addition to the other class of drugs
8 that clearly demonstrated benefit, which is of
9 course statins.
10 In terms of the population, it is and it
11 should be prescribed only to those at high or very
12 high risk whether or not they have HeFH. And I
13 have no [indiscernible] position regarding those
14 who may not tolerate statins however you define
15 tolerance.
16 I think we need to be pragmatic and
17 recognize that in many cases, it's hard to follow
18 the strict criteria that have been defined, but you
19 won't get patients to get on two, three, four
20 statins, and this is an option that we have now.
21 Thank you.
22 DR. SHAMBUREK: I'm Robert Shamburek. I

1 voted yes. I think the risks and benefits was the
2 major factor in my decision. We do need more data
3 on how this antibody works from safety and long
4 term. I think the genetics and the mechanism of
5 action was important in supporting this
6 first-in-class drug.
7 I do agree without outcome data, we can only
8 justify it looking at all the things and patients
9 with a current unmet need prior to waiting for an
10 outcome trial.
11 I voted for LDL as a surrogate on a
12 conditional basis of the mechanism, and I'm not
13 advocating LDL as a surrogate for all drugs having
14 an effect on LDL levels.
15 In the particular groups that I think are
16 groups should be targeted, I think we've heard that
17 the heterozygous FH, a group at very high risk and
18 potential benefit in the time, these patients
19 should have high LDL levels and on maximally
20 tolerated statins. I do qualify this that if
21 they're on a maximally tolerated one and they
22 become truly intolerant, I think it should

1 potentially be available to that particular group.
2 I also recognize that putting the class of
3 being heterozygous FH might be difficult for
4 labeling by the FDA. We heard from the public
5 today that some of them don't know or it took a
6 while for them to be categorized.
7 So despite the fact that we've heard, there
8 has been limited data, probably on the highest risk
9 ones. We heard a lot about 500 or so patients with
10 heterozygous FH. It would be nice to have more on
11 the high-risk patients.
12 Perhaps in the meantime, if we do have high
13 risk patients who have continuing cardiovascular
14 events, that could be part of what we call the high
15 risk heterozygous FH patients since we probably
16 have no U.S. engulfing data or definition of
17 heterozygous FH.
18 I think on the other categories, we heard
19 some provocative data, but we need more safety,
20 more long term. So I wouldn't advocate it in a
21 mixed hyperlipidemia for those with moderate risk.
22 Right now, I don't think we could advocate

1 monotherapy or the lack of a cohesive definition of
2 statin intolerance. But I do concur that the
3 results of the outcome trial are vital, and those
4 will be needed to consider expanding the use of
5 this class of drugs.
6 I certainly want to reiterate, which I think
7 everyone does, that I hope any approval will need
8 to lead to dropouts in the outcome trial so that we
9 can successfully get more data that we can use.
10 DR. SAGER: Philip Sager. I voted yes. I
11 was really focused on the very large unmet medical
12 need here for patients who are high risk, and that
13 it's more likely than not that this drug will
14 actually be able in those patients to reduce
15 cardiovascular outcomes.
16 I do acknowledge the uncertainty in not
17 knowing what the cardiovascular outcomes study will
18 actually show, but was unwilling to wait until 2017
19 or 2018 to actually get those results, given that
20 there's a very large number of patients who really
21 have a terrific unmet medical need.
22 I would be focused on patients who have

1 heterozygous FH or high or very high cardiovascular
2 risk who are receiving statins, hopefully maximally
3 tolerated statins is how I would phrase it, and who
4 still have high LDL-C cholesterol levels.
5 I think the labeling really needs to
6 emphasize not reducing or eliminating statin
7 therapy when this drug is used. And I'd also like
8 to just take this opportunity to commend the
9 sponsors on, I think, a really well thought out
10 continued development program, the outcomes study,
11 the cognitive study, as well as the whole
12 pharmacovigilance program. Thank you.
13 DR. NASON: My name is Martha Nason. I
14 voted no. I think my reasons echo Dr. Thomas' sort
15 of the most closely. Principally, I think the size
16 and short term of most of the data in the safety
17 database is concerning to me. Like Dr. Thomas, I
18 don't put much stock in 12-week safety data for
19 many of the things that might be concerning.
20 Certainly, there are some things you might see that
21 quickly, but there are other things you might not
22 see that quickly.

1 Another important part, I think, of my
2 rationale is that I, like everyone else around the
3 table, believe the cardiovascular outcomes trial is
4 very important, and my concern would be that if
5 this were available fairly widely that that really
6 would hamper the ability to recruit -- well, you've
7 said it's fully recruited, but to follow those
8 people and really get your answer.
9 I would imagine there would be a lot of
10 crossover and a lot of dropout, probably more than
11 you'd modeled, if suddenly this drug looks this
12 promising and is available. I think it'd be very
13 hard to really get clean answers from that trial,
14 and I think we really need those clean answers.
15 The only group -- similar to what other
16 people have said, the group that I hesitate the
17 most in is the heterozygous FH. I can certainly
18 see the arguments either way. I certainly am a bit
19 more on the fence with those folks, but I come down
20 to a feeling like for those people, too, we just
21 need more safety data.
22 If it's really as widespread and as maybe

1 hard to diagnose and hard to define as it sounds
2 like it might be, I think that might be hard to see
3 the important safety signals after it was licensed
4 for those people or to define exactly who got it.
5 And I think those people need to know that this
6 drug they're getting is as best we can, that we
7 have safety data and that it's safe in those
8 people.
9 DR. SMITH: Thank you all. We'll progress
10 to question 6, which is the second voting question.
11 I'll read the question.
12 Has the applicant sufficiently established
13 that the LDL-C lowering benefit of evolocumab
14 exceeds its risks to support approval for
15 homozygous familiar hypercholesterolemia?
16 the choices are yes, and if you vote that,
17 please explain your rationale. If you vote no,
18 please describe what further studies you believe
19 the applicant must conduct to establish a favorable
20 benefit/risk to support approval.
21 Any questions about the question?
22 (No response.)

1 DR. SMITH: Okay. Then the voting is open.
2 (Vote taken.)
3 DR. SMITH: The voting is now closed. The
4 DFO will read the results.
5 DR. BAUTISTA: The committee has voted
6 unanimously yes, 15 yeses, zero noes, zero
7 abstentions.
8 DR. SMITH: Okay. And so again, ask you to
9 state your name, your vote, and your rationale.
10 And Dr. Nason, we'll come right back to you to
11 start off this time.
12 DR. NASON: I'm still Martha Nason. This
13 time I voted yes. I don't want to seem
14 inconsistent. To me, the biggest difference,
15 besides the unmet need, is that it is a smaller
16 population. It will be a little more centralized,
17 I think, as far as monitoring for looking for
18 safety signals as far as their ongoing care.
19 Although I would love more safety data in
20 these people, too, the size of the population, the
21 limited population makes that pretty much an
22 impossible endeavor or a very difficult endeavor.

1 So to me, that was what changed my mind as
2 compared to the heterozygous case. For the
3 heterozygous, I think you can get more safety data
4 for these folks. It's going to be tough to get
5 much more, and clearly, the unmet need is enormous.
6 Just the last thing I wanted to say, though,
7 is I do think you should continue to study the idea
8 of the more frequent dosing. I would say I approve
9 it for the monthly dosing. I think the idea of the
10 two weekly -- sorry -- twice a week -- no -- every
11 2 weeks -- biweekly, thank you -- is something that
12 there could easily be another study following up on
13 to look at whether that really is a benefit and for
14 whom in the homozygous population.
15 DR. SAGER: Philip Sager. I voted yes. The
16 pathophysiologic mechanism in patients with
17 homozygous FH is the inadequacy of their LDL
18 receptors and their very high LDL-C cholesterol,
19 and lowering that will almost certainly be of
20 clinical benefit.
21 DR. SHAMBUREK: Bob Shamburek. I voted yes.
22 Homozygous FH is devastating, and we heard from

1 several families. The families are desperate for
2 treatment. There is no treatment that will give
3 them a normal LDL goal at this time. The
4 homozygous FH patients have multiple drug and
5 treatment options from LDL apheresis to two
6 recently approved drugs. And we heard on three,
7 four different additional drugs.
8 It's not entirely clear how all these will
9 now interact. We don't have exposure with some of
10 these newer or other drugs. However, I think there
11 is a very important unmet need.
12 Intuitively, when you look at patients who
13 have very little or none, you would expect the
14 response would be less, although any significant
15 response will do a benefit.
16 I think we heard some reservation about will
17 patients who really don't gain a benefit continue,
18 but I think in the U.S., most of those patients go
19 to major lipid centers or hope that will be the
20 situation.
21 I applaud and go for the favor for using
22 adolescents. I think the adolescents before they

1 develop the need for bypass and disease that may
2 not be prevented can potentially have the greatest
3 benefit. And once we have some outcome data, I
4 hope it will even go to a younger age.
5 I do have a little concern that we don't
6 have enough data with the 420-milligram Q2 week,
7 and it may just be we don't have enough data that
8 going from the 4 week to the 2 week, the 6 percent
9 incremental reduction, which is 25 milligrams per
10 deciliter, in a patient who might start at 800 or
11 1,000, it could make a difference. But I think
12 right now, I can't really fully support that, but I
13 think it will be another armament in the treatment
14 of homozygous FH.
15 DR. ROSENBERG: Yves Rosenberg. I voted yes
16 for the argument that's just been expressed. It's
17 a clear no-brainer here that the benefit clearly
18 exceed any potential risk, that the physiopathology
19 is clear relating the high LDL with the
20 cardiovascular outcome.
21 I do agree that we still need to clearly
22 define the potential risk. We also, as soon as

1 possible, need to study pediatric population. And
2 we do also need further study to further define the
3 optimal dosage and dosing schedule in this
4 population.
5 DR. WILSON: Peter Wilson. I voted yes.
6 For those of us who have treated youngsters and
7 teenagers and adults with homozygous FH, as was
8 just said by Dr. Shamburek, they need everything we
9 can offer them, absolutely everything. And LDL
10 lowering offers the word that was perhaps said more
11 than anytime by all of the speakers, it offers
12 hope.
13 DR. HIATT: William Hiatt. I voted yes. I
14 was part of the lomitapide review several years ago
15 and understand the severity of this phenotype, the
16 limited options, the extreme challenge in doing a
17 randomized control trial. I think the
18 context-specific decision to vote yes made sense.
19 DR. SMITH: I'm Robert Smith. I voted yes
20 for the kinds of reasons that I stated in the
21 previous question and what I've heard so
22 effectively stated by the people who have preceded

1 me here.

2 It's fundamentally addressing an unmet need

3 in a very severe clinical situation with a new

4 class of drugs that, thus, has promise and is worth

5 the risks that accompany uncertainty about its

6 ultimate effects on outcome and uncertainty about

7 the side effects.

8 I don't feel strongly about the dosing. I

9 do agree with the other members of the panel who in

10 their conclusions that there really is not

11 convincing evidence that the higher dose is more

12 effective, but the goal here is maximum effect in a

13 very critical disease situation. I wouldn't feel

14 comfortable restricting dose either.

15 So I think it's -- I guess I would go with

16 Dr. Rosenberg's comment. I would like to somehow

17 see whatever more we can learn about dosing to have

18 a maximally effective dose.

19 DR. BLAHA: Michael Blaha. I voted yes. I

20 compliment my co-panelists on some eloquent

21 remarks, and I'll try to make some more.

22 I'm really voting here as a both scientist

1 but also as a physician who, of course like the
2 rest of you, sees patients sometimes with
3 homozygous FH, who is involved in their care and
4 knows how severe this phenotype is, and that we
5 really need everything we can for these patients
6 and how exciting it is that we're able to get some
7 of these patients down to LDL levels that we
8 haven't really seen before and be able to offer
9 hope for these patients. I think it's really an
10 exciting time, and we've waited for this for a long
11 time.
12 As far as the dosing goes, I'm in support of
13 the Q2 week dose. I think in expert hands, which
14 is where this will be used, in lipid clinics, it
15 will be a potentially powerful tool for those
16 patients with high PCSK9 levels in which a more
17 frequent dosing may be of benefit. And I think
18 that can be worked out by expert hands, and I think
19 it's a tool that will be used, I think,
20 appropriately and we'll learn a lot from.
21 DR. THOMAS: Abraham Thomas. I voted yes.
22 Just a few of my points. I still think right now

1 it's monthly dosing, and I would suggest that we
2 just need a longer time to observe that the
3 decrement is real. But I would also suggest in the
4 original study that was presented, the group that
5 had maximal effect at four weeks did not get an
6 increased frequency of dosing.
7 I don't see why they shouldn't be also given
8 the opportunity to have increased frequency of
9 dosing and see if they also get a decrement.
10 Another 6 percent in that group would also be
11 helpful, but I don't think it should just be
12 limited to the ones who are non-responders in the
13 future studies.
14 I have concerns about the pediatric
15 population because it's a new drug, and we don't
16 know all the risks. However, that should not limit
17 them from getting it because of the devastating
18 disease.
19 If I remember, 35 to 45 percent of those
20 pediatric patients already had cardiovascular
21 disease in that population, and we're trying to
22 prevent further events in some of them.

1 Finally, I just wanted to thank the public
2 speakers. I think it adds a lot to what we do and
3 discuss because it really is about patients. And
4 the FDA always does a good job. I expect them to
5 do a good job, so we never really thank them for
6 their job.
7 The sponsors did a really good job, which
8 isn't always the case. I would like to thank the
9 sponsors for really being on top of their
10 presentations.
11 In this disease, LDL really is the hallmark.
12 So if there is a surrogate, LDL is the one in this
13 specific disease. I am perfectly correct with
14 Dr. Hiatt and Wilson and some others that LDL may
15 not be the appropriate surrogate for other
16 diseases, but in this one, it really is, and that's
17 proven the test of time.
18 DR. BURMAN: Ken Burman. I voted yes. I
19 agree with Dr. Thomas' and everybody else's not
20 only opinions but also laudatory comments regarding
21 all of the participants. This disease is extremely
22 serious with limited options at present, and all

1 efforts should be made to lower LDL to the extent
2 possible.
3 I'm concerned about evolocumab use in young
4 teenagers and also with possible other long-term
5 effects such as relating to glucose metabolism,
6 puberty, neurocognitive issues, and CV events. I
7 think it prudent that genetic analysis should be
8 performed on these patients to confirm the
9 diagnosis and give specific information relating to
10 the number of LDL receptors. And I think both dose
11 options should be available. Thank you.
12 MS. MCCALL: Debra McCall. I voted yes for
13 all the reasons everybody's already stated and also
14 because patients and their physicians need another
15 option.
16 DR. ORZA: Michele Orza. I voted yes for
17 the reasons that have been well articulated by
18 others, and would just add that I am a little bit
19 troubled by the lack of data for understandable
20 reasons, because it's a rare condition and it's a
21 small population.
22 But perhaps in this instance, something like

1 a registry could be helpful moving forward to get
2 more data on these patients and this drug in this
3 population.
4 CAPT BUDNITZ: Dan Budnitz. I voted yes,
5 and will just add that this may be a population to
6 get signals from adverse events unlikely to
7 outweigh the benefits in this population but might
8 inform others down the road.
9 DR. STANLEY: This is Charles Stanley. I
10 voted yes. As a pediatrician, I wanted to
11 particularly congratulate the sponsor for
12 supporting this indication for really an orphan
13 disease, which pediatricians first see. And I
14 think the unmet need here, as people have said, is
15 so great that the adverse event profile -- safety
16 profile here certainly justifies proceeding with
17 this indication.
18 DR. COOKE: I'm David Cooke. I voted yes.
19 I'm going to speak in a little bit more detail
20 about the potential pediatric indication.
21 Unambiguously, I support its use in those children
22 12 to 18 that are post-pubertal. I think that's

1 very clear.
2 I understand that we wouldn't be able to
3 approve this for children under 12 since they
4 haven't been studied, and certainly, the
5 appropriate dosing as you get to smaller and
6 smaller children would need to be determined. But
7 I think even in those younger children, there
8 clearly remains a very large unmet need so that
9 really a modest amount of data could potentially be
10 appropriate for its approval down in that age
11 range.
12 We have knowledge that the appropriately
13 sensitive tissues have the capacity for de novo
14 cholesterol synthesis, the brain, the adrenal
15 gland, the gonads. I think even the data from -- I
16 don't remember whether it was this trial or
17 yesterday's agent that demonstrated a lack of even
18 profound LDL suppression on steroid hormone
19 synthesis in the adults that were studied is more
20 reassuring data that's added to the accumulating
21 data with statins in even young children in the
22 safety of them.

1 So again, can't approve it down to younger
2 children yet, but I would encourage those
3 investigations to happen as soon as possible.
4 I think the area that may be a little
5 uncertain would be the 12- to 18-year-old children
6 who are not post-pubertal, the pre- or peripubertal
7 children in that age range. And although I don't
8 think we have data from this study to answer the
9 question of the impact on puberty, I think the data
10 from the statins is sufficient to translate into
11 those children that I would be comfortable using
12 this agent in the non-post-pubertal 12- to 18-year-
13 old children, although I certainly would encourage
14 future studies to actually make that distinction
15 and accumulate that data.
16 DR. SMITH: Thank you.
17 Dr. Albrecht, would you like to make any
18 comment?
19 DR. ALBRECHT: Thank you for kind offer. I
20 would align with most of the comments made in
21 support of the yes votes. And I'd like to make one
22 additional comment, if I may.

1 Considering that data in homozygous FH
2 patients are very hard to come by and that there is
3 really no major safety concern, we should offer
4 physicians in the labeling 2 doses because this is
5 an orphan population, very small and difficult to
6 treat population in which treatment needs to be
7 individualized. And for that purpose because the
8 data do at least not say it's bad, so we should
9 offer the physicians in the labeling the option to
10 try out different doses.
11 DR. SMITH: Yes, Dr. Sager?
12 DR. SAGER: I just wanted to add I didn't
13 address the biweekly dosing issue in my comments.
14 I would be strongly in favor of that being
15 available. Homozygous FH patients are managed by
16 real experts, and I think being able to
17 individualize the dosing regimen in those patients
18 would result in better patient management.
19 DR. SMITH: Would the FDA like to many any
20 final comments today?
21 DR. J. SMITH: We would just like to thank
22 you-all very, very much for your stamina and for

1 all the discussion over the last couple days. We
2 have found it incredibly helpful, which is why
3 you're here, and we genuinely appreciate the time
4 that you give to review the materials and to engage
5 with each other. We furiously take notes, and we
6 discuss at length afterwards. And it will inform
7 our decision-making going forward. So thank you
8 very much.

9 **Adjournment**

10 DR. SMITH: I would like to thank the
11 sponsor for your careful and thoughtful and helpful
12 presentations, the FDA for the same and what you
13 provided us for information. I want to thank the
14 open public hearing speakers for your efforts to
15 get here and your contributions, which also are
16 very important, and, of course, the panel members
17 for all the thought you've given this and the input
18 you've had as well. So given that, I will say this
19 meeting is adjourned.
20 (Whereupon, at 4:40 p.m., the meeting was
21 adjourned.)
22